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THE SYNTHESIS OF STREPTOSE AND RELATED COMPOUNDS

A THESIS

Presented to

The Faculty of the Graduate Division

by

William Edward McGonigal

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THE SYNTHESIS OF STREPTOSE AND

RELATED COMPOUNDS

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TABLE OF CONTENTS

LIST OF CHARTS

LIST OF TABLES

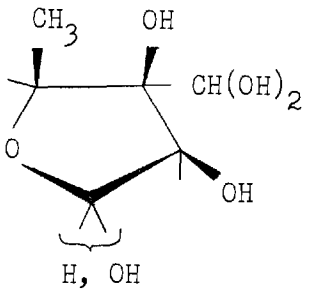
LIST OF FIGURES

GLOSSARY OF ABBREVIATIONS

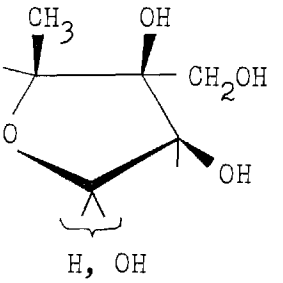
A.I.P.	Argon Inlet Pressure (GLC).
APW-1	t-Amyl alcohol:n-propyl alcohol:water, 4:1:1 (v/v), paper chromatography solvent system.
APW-1.5	t-Amyl alcohol:n-propyl alcohol:water, 4:1:1.5 (v/v), paper chromatography solvent system.
BAW	t-Butyl alcohol:acetic acid:water, 2:1:1 (v/v), paper chromatography solvent system.
BEW	n-Butyl alcohol:ethanol:water, 4:1:1.5 (v/v), paper chromatography solvent system.
C.T.	Column Temperature (GLC).
DSS	Sodium 2,2-dimethyl-2-silapentane-5-sulfonate, n.m.r. standard.
EAW	Ethyl acetate:acetic acid:water, 9:2:2 (v/v), paper chromatography solvent system.
EGA	Ethylene glycol adipate, GLC column liquid phase.
GLC	Gas-liquid chromatography.
N	Ninhydrin spray reagent.
PC	Potassium permanganate-sodium carbonate spray reagent.
R.T.	Retention Time (GLC).
SE-30	Silacone GLC column liquid phase.
SP	Sodium metaperiodate spray reagent.
TLC	Thin-layer chromatography.
TMS	Tetramethylsilane, n.m.r. standard.

SUMMARY

L-Streptose is the unusual branched-chain dialdehyde carbohydrate present, glycosidically bound, in streptomycin. Because the conditions necessary for the complete hydrolysis of streptomycin destroy the streptose fragment, it has never been isolated. On the basis of the properties and structures of several transformation products, the structure of streptose was indicated to be 3-C-formyl-5-deoxy-L-lyxose.



L-Streptose



L-Dihydrostreptose

No successful synthesis of L-streptose, L-dihydrostreptose (present in dihydrostreptomycin) or any of the known derivatives of the intact streptose molecule has been reported. Because of the importance of streptomycin, as well as the unusual nature of streptose, the purpose of this research was to perform a structurally definitive synthesis of the structure assigned to L-streptose. The identity of the product was to be shown by its conversion into several of the known derivatives of L-streptose. Since the other fragments of the streptomycin molecule, streptidine and N-methyl-L-glucosamine, have been synthesized, the synthesis of streptose would complete the synthetic verification of the structure of streptomycin

except for the glycosidic linkages.

L-Rhamnose was degraded by known procedures to 5-deoxy-L-arabinose, acetonation of which afforded the known crystalline 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose (I). This material showed physical properties that were identical to those described in the literature. Compound I was further characterized by means of syrupy 3-O-benzoyl, crystalline 3-O-(3,5-dinitrobenzoyl), and crystalline 3-O-(p-toluenesulfonyl) derivatives. The n.m.r. spectra of I and its derivatives strongly support the previously known structure of I and make possible the assignment of the β anomeric configuration to all four compounds.

Because the oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside with chromium trioxide-pyridine gave 21-46 per cent yields (with 39-36 per cent concurrent recoveries of starting material) of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose (II) (characterized by infrared and n.m.r. spectra and by a crystalline oxime derivative), a number of attempts were made to oxidize I with this reagent, without success. In addition, attempted oxidations of I using chromium trioxide in acetone, aluminum t-butoxide with either acetone or quinone, and platinum and oxygen were unsuccessful. Attempted oxidation of the 3-O-(p-toluenesulfonyl) derivative of I using dimethyl sulfoxide was also unsuccessful. The oxidation of I to 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose (III) was finally achieved using N,N'-dicyclohexylcarbodiimide, pyridinium phosphate, and dimethyl sulfoxide at room temperature. These mild conditions have previously been shown to effect selective oxidation of secondary alcohols to ketones. Compound III was obtained in yields of 51-72 per cent and was characterized by infrared and n.m.r. spectra

and by a crystalline oxime derivative.

The Grignard addition of vinylmagnesium bromide to II was performed and gave a 55 per cent yield of crystalline methyl 2,3-O-isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside (IV). That only the talo configuration was produced was indicated by GLC analysis of the crude reaction product and an analysis of the n.m.r. spectrum of purified IV. Similar specificity of addition was observed when the reaction between vinylmagnesium bromide and III gave only crystalline 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (V) in 70 per cent yield. That only the lyxo configuration was produced was indicated by GLC analysis of the crude reaction product and the n.m.r. spectrum of purified V.

Compound IV was ozonolyzed in methylene chloride solution at -80° in the presence of pyridine and gave syrupy methyl 2,3-O-isopropylidene-4-C-formyl-6-deoxy-α-L-talopyranoside, which was characterized by infrared and n.m.r. spectra. A similar ozonolysis of V was not successful. However, when the ozonide of V was prepared in ethyl acetate solution at -80° and decomposed with sodium borohydride, there was obtained a 71 per cent yield of crystalline 1,2-O-isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose (VI). Compound VI was characterized by infrared and n.m.r. spectra. The hydrolysis of VI to give L-dihydrostreptose was effected by stirring with aqueous Dowex 50W-X8 (H^+) for two days at room temperature. After chromatography over carbon-celite, L-dihydrostreptose was obtained in 63 per cent yield as a colorless, reducing syrup. The n.m.r. spectrum of the syrup indicated the presence of two anomeric C_4 furanoses. The compound showed a satisfactory infrared spectrum and was chromatographically homogeneous on paper in two solvent

systems. Synthetic L-dihydrostreptose was oxidized by bromine water and gave L-dihydrostreptosonic acid lactone in 60 per cent yield. After crystallization, L-dihydrostreptosonic acid lactone showed physical and spectral properties that were in agreement with those reported in the literature for naturally derived samples of this compound.

Decomposition of the ozonide of V was also accomplished using hydrogen and palladium. The syrupy product, 1,2-O-isopropylidene-3-C-formyl-5-deoxy-β-L-lyxofuranose (VII) rapidly polymerized, as evidenced by the virtual disappearance, on standing, of the n.m.r. absorption of the aldehyde hydrogen as well as the decrease in the intensity of the infrared absorption of the aldehyde carbonyl group. In addition, the material was insoluble in both water and carbon tetrachloride after standing at room temperature for one day. That no great structural change was involved in the polymerization was shown by the sodium borohydride reduction of VII, which gave VI in 55 per cent yield. Polymeric VII was deacetonated by stirring at room temperature for two days in water-dioxane solution with Dowex 50W-X8 (H^+) and furnished in 67 per cent yield after chromatography on carbon-celite, L-streptose, a colorless glass. Synthetic L-streptose showed a satisfactory infrared spectrum and was chromatographically homogeneous on paper in two solvent systems. The n.m.r. spectrum of L-streptose indicated the presence of two anomeric C_4 furanose aldehyde hydrates. The observation that synthetic streptose gave no maltol on treatment with alkali while VII did, is consistent with the previously proposed requirement for this rearrangement of a glycosidic substituent at C_1 of L-streptose.

Synthetic L-streptose was oxidized by bromine-water and gave

L-streptosonic acid monolactone in 50 per cent yield. That the physical and spectral properties of this material were identical to those of a naturally derived sample proves the identity of the synthetic L-streptose obtained.

The synthesis of L-streptose and L-dihydrostreptose employed proves that the absolute configuration of these compounds is D(S) at C_2 and L(R) at C_4. That the configuration at C_3 is D(R) is indicated by the expected course of the reactions employed, the model compounds studied herein, and the n.m.r. spectra of the intermediate compounds. The results of this synthesis together with those obtained by another worker in these laboratories prove that the configuration at C_3 of L-streptose is D(R).

The synthesis of L-streptose completes the synthetic proof of structure of streptomycin except for the glycosidic linkages and makes possible a plan for the total synthesis of streptomycin.

Because of an interest in the rapidly developing area of the chemistry of amino sugars, a new 4-amino-4,6-dideoxy-L-hexose was synthesized. Reaction of the known methyl 2,3-O-isopropylidene-4-O-(p-toluenesulfonyl)-α-L-rhamnopyranoside with sodium azide in boiling dimethyl formamide, followed by reduction of the azido group of the product with lithium aluminum hydride, furnished methyl 2,3-O-isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranose which was isolated as the crystalline hydrochloride (VIII). While the direct acid hydrolysis of VIII failed, the acid hydrolysis of the N-acetyl derivative of VIII yielded a small amount of unstable crystalline 4-amino-4,6-dideoxy-l-talose.

CHAPTER I

INTRODUCTION

Streptomycin

Streptomycin was first isolated in crude form from cultures of Streptomyces griseus originally obtained from the soil (1). Because the substance was strongly bacteriostatic against a wide variety of microorganisms and had low toxicity, its production and pharmacology have been studied extensively (2). The literature concerning the isolation and early development of streptomycin has been reviewed (1). Streptomycin was the first drug to be proved effective against tuberculosis (3) and has also been used effectively against many other diseases, among which are leprosy, tularemia, typhoid fever, and brucellosis (2,4). In terms of production, medical usage, and medicinal effectiveness, streptomycin and related antibiotics have for a number of years been second in importance only to the penicillins (2).

Streptomycin was shown to be a water-soluble basic compound that was sensitive to both acids and bases (1). The difficulties encountered in purifying the compound caused considerable discrepancies in the results of early molecular weight and molecular formula determinations. The molecular formula was finally established as $C_{21}H_{39}N_7O_{12}\cdot 3HX$ for streptomycin salts (2).

Structure of Streptomycin

Carbonyl reagents and oxidizing agents were shown to inactivate

streptomycin (5,6). Hydrogenation of streptomycin trihydrochloride (one mole of hydrogen was consumed) yielded dihydrostreptomycin, which had only slightly different biological activity, an extremely rare occurrence, since slight structural changes in most antibiotics usually result in the destruction of activity (2,7). More recently, dihydrostreptomycin has been shown to be a major fermentation product of Streptomyces humidus (8). Dihydrostreptomycin was not inactivated by carbonyl reagents (7). The formation of oxime and semicarbazide derivatives of streptomycin further substantiated the presence of a free (or potentially free) carbonyl group (5,9). Streptomycin showed no carbonyl absorption in the ultraviolet or infrared regions (2,10). Vigorous alkaline hydrolysis of streptomycin yielded maltol (2-methyl-3-hydroxy-4(H)-γ-pyrone) (11). Kuhn-Roth determination indicated that streptomycin possesses one C-methyl group (12).

Degradation of streptomycin with hydrogen chloride in methanol yielded, after chromatography, two compounds that were named streptidine dihydrochloride (I) and methyl streptobiosaminide hydrochloride dimethyl acetal (II) (5,9).

$$\underset{C_{21}H_{39}N_7O_{12}\cdot 3HCl}{\text{Streptomycin}} \xrightarrow[CH_3OH]{HCl} \underset{\text{I}}{C_8H_{18}N_6O_4\cdot 2HCl} + \underset{\text{II}}{C_{13}H_{22}NO_7(OCH_3)_3\cdot HCl}$$

Streptidine was observed to be an optically inactive strongly basic compound that had a molecular formula of $C_8H_{18}N_6O_4$ (2). Chemical and physical evidence, and the properties and identity of certain derivatives showed that streptidine is the 1,3-diguanidino-2,4,5,6-tetrahydroxycyclohexane isomer that has all of the groups equatorial (the scyllitol configuration) (2,13,14,15). It has also been shown that the C_4 hydroxyl group of

streptidine is attached to the streptobiosamine moiety (16). Streptidine has been synthesized (15) and the absolute stereochemistry of the six asymmetric carbon atoms of streptidine in the intact streptomycin molecule has been determined (17). Since streptidine does not possess a free or potentially free carbonyl function, the carbonyl group of streptomycin resides in the streptobiosamine moiety and was converted into the dimethyl acetal upon methanolysis.

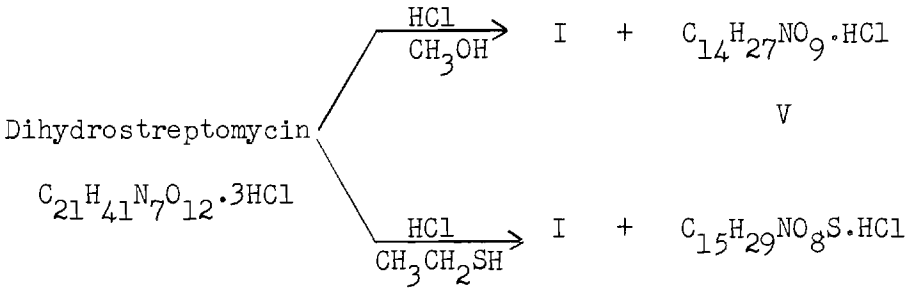
Streptomycin was oxidized with bromine water and gave an acid, which upon methanolysis gave I and a substance that contained two O-methyl groups. This new material showed absorption at 5.77 μ (ester carbonyl) in the infrared region (7). Basic hydrolysis removed only one of the methoxy groups. Acetylation of the amorphous hydrolysis product gave a crystalline tetraacetate, $C_{13}H_{19}NO_{10}(COCH_3)_4$. Since bromine water oxidation produced an acid that has the same number of carbon atoms as streptobiosamine, it was indicated that the "free" carbonyl group of streptomycin is an aldehyde.

Reaction of streptomycin with hydrogen chloride in ethanethiol yielded I and ethyl thiostreptobiosaminide diethyl dithioacetal (III) (18). Two acetylated isomers ($C_{27}H_{45}NO_{11}S_3$; m.p. 80.5-81°, $[\alpha]_D$ -192°

$$\text{Streptomycin} \xrightarrow[CH_3CH_2SH]{HCl} \text{I} + \underset{\text{III}}{C_{19}H_{37}NS_3O_7 \cdot HCl}$$

and m.p. 111-111.5°, $[\alpha]_D$ -29°) of III could be obtained that presumably differed only in anomeric configuration (12). Desulfurization of either isomer gave, after reacetylation, the same product, tetraacetyldideoxydihydrostreptobiosamine, IV ($C_{21}H_{33}NO_{11}$) (12,19).

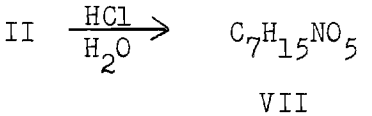
Dihydrostreptomycin gave I and methyl dihydrostreptobiosaminide hydrochloride (V) upon methanolysis (9) and gave I and ethyl thiodihydrostreptobiosaminide hydrochloride (VI) upon mercaptolysis (18).



The above results of the degradations of streptomycin and dihydrostreptomycin were observed to be consistent only with the conclusions that the "free" carbonyl group of streptomycin is aldehydic and that streptidine is glycosidically attached to another aldehyde group in streptobiosamine (2,12).

Since II formed an N-nitroso derivative, and upon vigorous alkaline hydrolysis yielded methylamine, it was concluded that the nitrogen atom in streptobiosamine was present as a methylamino group (5,9).

Aqueous acid hydrolysis of II, followed by acetylation, gave a compound, $C_{17}H_{25}NO_5$, the formula of which was satisfactory for an N-methylhexosamine pentaacetate (20). Chemical and physical evidence obtained for this compound and certain derivatives indicated that the parent fragment was N-methyl-L-glucosamine, VII (2,20). This was confirmed by synthesis (20).



Partial deacetylation of IV yielded N-acetyldideoxydihydrostreptobiosamine, VIII ($C_{14}H_{28}NO_8$), which gave no reducing tests (18). Since vigorous acid hydrolysis of VIII produced N-methyl-L-glucosamine, it was concluded that the amino sugar was glycosidically attached to the other carbohydrate moiety in streptobiosamine (18). The other carbohydrate portion of streptobiosamine was named streptose (18).

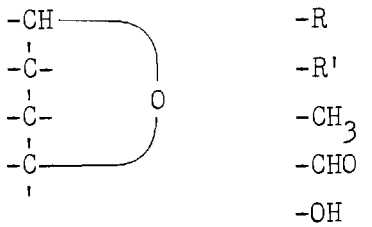
Mathematical manipulation of the molecular formulas of streptomycin, streptidine, and N-methyl-L-glucosamine revealed that streptose has a molecular formula of $C_6H_{10}O_5$ (18).

	C_{21}	H_{39}	N_7	O_{12}	Streptomycin
-	C_8	H_{18}	N_6	O_4	Streptidine
-	C_7	H_{15}	N	O_5	N-Methyl-L-glucosamine
+		H_4		O_2	Two moles of water
	C_6	H_{10}		O_5	Streptose

It was recognized that streptose must have two aldehyde (or potential aldehyde) groups and one C-methyl group to account for all of the data. Therefore streptose must have a branched carbon chain and a tertiary hydroxyl group (2,9). It was observed that the tetraacetates of II and III showed absorption at 2.85 and 2.75 μ, respectively, in the infrared region (9,18). In addition, the tetraacetate of II liberated one mole of methane in the Zerewitinoff determination (9).

All of the above data concerning the structural formula of streptose in streptomycin are summarized in partial structure IX.

Aqueous acid hydrolysis of tetraacetyldideoxydihydrostreptobiosamine (IV) yielded VII and a new crystalline compound $C_6H_{12}O_3$,

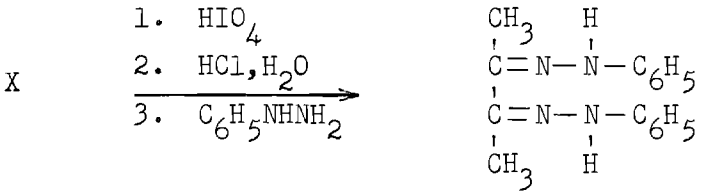


R = Streptidinyl

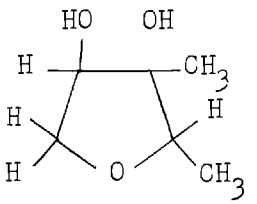
R' = N-Methyl-L-glucosaminyl

IX

dideoxydihydrostreptose (X) (19,21). Periodic acid oxidation of X, followed by acid hydrolysis and treatment of the solution with phenylhydrazine gave the phenyl osazone of biacetyl (19,21). Compound X formed a



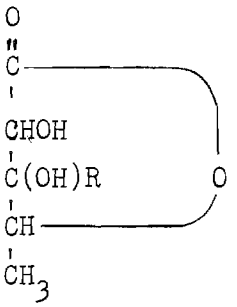
di-p-nitrobenzoate and enhanced the acidity of boric acid solutions (19). These data show that X must be a 3,4-dihydroxy-2,3-dimethyltetrahydrofuran and that the hydroxyl groups are probably cis.



X

Reaction of the tetraacetate of III with mercuric chloride removed the thioethyl groups and gave crystalline tetraacetylstreptobiosamine (XI)

(22). Compound XI could be catalytically reduced to give tetraacetyldihydrostreptobiosamine, XII ($C_{21}H_{31}NO_{13}$) (23). Reacetylation of XII gave hexaacetyldihydrostreptobiosamine ($C_{25}H_{37}NO_{15}$), which was identical to that obtained after acetylation of the product from mercuric chloride treatment of the pentaacetate of VI (23). Compound XI was oxidized with bromine water and furnished, after reacetylation, a new crystalline compound, pentaacetylstreptobiosamic acid monolactone, XIII ($C_{23}H_{31}NO_{15}$) (22). Aqueous-acid hydrolysis of XIII gave VII and a crystalline compound, XIV ($C_6H_8O_6$) designated streptosonic acid monolactone (22). The infrared spectrum of XIV showed absorptions at 5.62 and 5.80 μ. The compound had neutralization and saponification equivalents of 175 and 87.5, respectively (theoretical, 176 and 88), and under the appropriate conditions formed a crystalline diamide ($C_6H_{12}N_2O_5$) and a crystalline diacetate ($C_{10}H_{12}O_8$). Compound XIV gave a positive iodoform test. The diamide of XIV consumed two moles of periodic acid and gave acetaldehyde, but no formic acid. Compound XIV likewise consumed two moles of periodic acid and gave glyoxylic acid and oxalic acid. Thus there is only one possible structure for XIV (22).

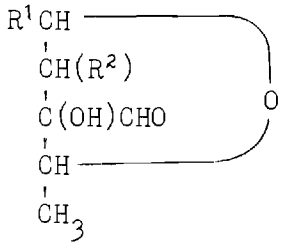


XIV, R = CO_2H

XV, R = CH_2OH

Compound XII, when treated with bromine water followed by aqueous-acid hydrolysis, gave VII and a new compound, XV ($C_6H_{10}O_5$) designated

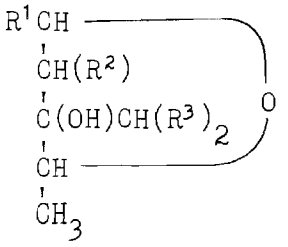
dihydrostreptosonic acid lactone (23). This compound could also be prepared in a similar manner from the product of mercuric chloride treatment of the pentaacetate of VI (23). Compound XV behaved as a lactone on potentiometric titration, showed absorption at 5.65 μ in the infrared region, and when oxidized by two moles of sodium periodate, gave formaldehyde (23). These data, together with the above results, placed the carbonyl group of streptomycin at the branched position of streptose (23). The structural formulas of the compounds discussed are shown below.



Streptomycin, R^1 = Streptidinyl;

R^2 = N-Methyl-L-glucosaminyl (VIIa)

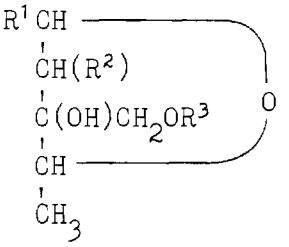
XI, R^1 = OH, R^2 = VIIb*



II, R^2 = VIIa; $R^1, R^3 = OCH_3$

III, R^2 = VIIa; $R^1, R^3 = SCH_2CH_3$

IV, R^2 = VIIb*, R^1, R^3 = H



Dihydrostreptomycin, R^1 = Streptidinyl;

R^2 = VIIa; R^3 = H

V, R^2 = VIIa; $R^1 = OCH_3$; R^3 = H

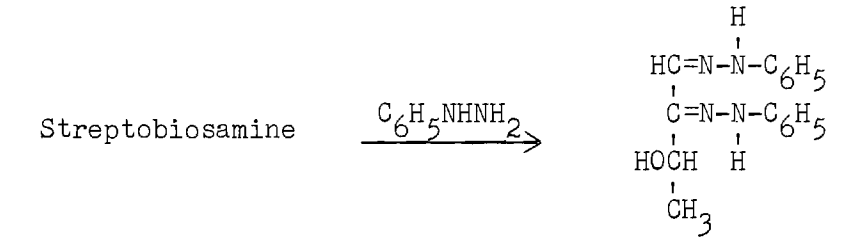
VI, R^2 = VIIa; $R^1 = SCH_2CH_3$; R^3 = H

The absolute configuration of streptose and derivatives remained to be determined. Mineral acid hydrolysis of streptomycin yielded I and

---

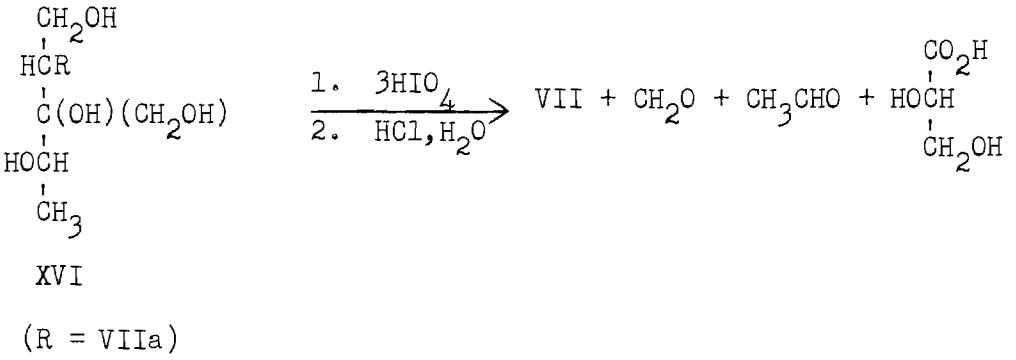
* The tetraacetate of VIIa.

crude amorphous streptobiosamine hydrochloride (24). The action of phenylhydrazine on the latter compound resulted in the formation of 4-deoxy-L-erythrose phenyl osazone, which was identified by synthesis (24). The application of Hudson's amide and hydrazide rules to the diamide of XIV



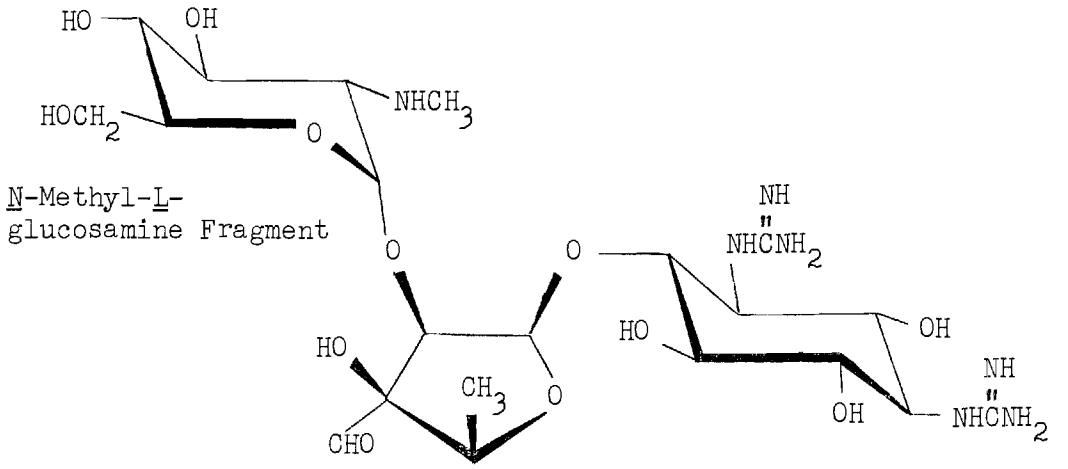
and hydrazide of XV (both are dextrorotatory) indicated that the configuration of the C_2 hydroxyl group was D (23).

Vigorous hydrogenation of N-acetylstreptobiosamine yielded crystalline N-acetyltetrahydrostreptobiosamine, XVI, which upon oxidation with periodic acid followed by aqueous acid hydrolysis, gave VII, one mole of formaldehyde, one mole of acetaldehyde, and L-glyceric acid (25). This result confirms both the position of attachment of N-methyl-L-glucosamine and the D configuration at C_2 of streptose.



Based on the fact that compound X enhanced the acidity of boric acid solutions, the C_2 and C_3 hydroxyl groups were designated cis in

streptose and derivatives (19). The absolute configuration of streptose in streptomycin is represented by XVII.



XVII

The configurations of the glycosidic unions in streptomycin were determined to be β in streptose and α in N-methyl-L-glucosamine (26). The fact that streptomycin possesses a potentially free carbonyl group has been indicated. It is likely that the carbonyl group of the streptose moiety is bound by a hemiacetal linkage to one of the free hydroxyl groups or the methylamino group of the N-methyl-L-glucosamine portion (27). The existence of different crystalline forms and the mutarotation of certain salts of streptomycin (10,28) indicate that probably at least two different hemiacetal linkages are possible (10).

Purpose of the Research

The structures and stereochemistry of streptidine and N-methyl-L-glucosamine have been confirmed by synthesis. Streptose, the unusual

branch chain carbohydrate component of streptomycin, has never been isolated or synthesized. Recently, the isolation of dihydrostreptose from mild hydrolysis of methyl N-acetyldihydrostreptobiosaminide was claimed (29). In addition, lithium aluminum hydride reduction of dihydrostreptosonic acid lactone was reported to yield a mixture of compounds, one of which was claimed to be dihydrostreptose (30). None of the derivatives of the intact streptose molecule has been synthesized. Streptose and hydroxystreptose (a component of the relatively minor antibiotic hydroxystreptomycin) are the only naturally occurring branched chain carbohydrates known that have a branch aldehyde function. It would be desirable, in view of the unusual and unique features of the molecule and the importance of streptomycin, to accomplish the synthesis of streptose. For such a synthesis to be structurally definitive, the stereochemistry of the product must be known and the material must be converted into one or more of the known derivatives of streptose.

The synthesis of streptose would complete the synthetic verification of the structure and stereochemistry of the three fragments of streptomycin and perhaps provide a starting point for the synthesis of streptomycin and the other antibiotics that contain streptose or related compounds (mannisidostreptomycin and dihydrostreptomycin).

The purpose of this research was to synthesize the structural formula assigned to streptose by a structurally definitive pathway.

CHAPTER II

EXPERIMENTAL

Apparatus and Techniques

Anhydrous methanol was prepared as described elsewhere (31). Anhydrous acetone was prepared by distillation from potassium permanganate and potassium carbonate and redistillation from anhydrous calcium chloride. Anhydrous ether was purchased (Merck reagent 71633) and stored over sodium ribbon. Redistilled benzene was dried by storage over sodium ribbon. Anhydrous pyridine was prepared by repeated distillation of purified pyridine (Matheson Coleman and Bell PX 2025) from potassium hydroxide pellets until the distillate did not turn yellow on storage over potassium hydroxide pellets. Petroleum ether (b.p. 30-60^{0}) was always redistilled. Ethyl acetate was dried by distillation from phosphorus pentoxide powder. Anhydrous tetrahydrofuran was always prepared by distillation (of Baker reagent 9450) from lithium aluminum hydride immediately prior to use. Isopropyl ether was dried by distillation from sodium and was stored over sodium ribbon.

Unless otherwise stated, all concentrations and evaporations were performed using a Rinco (Model VE-1000-A) rotating evaporator at water aspirator vacuum and temperatures below 50^{0}. Drying of solutions and extracts in organic solvents was accomplished, unless otherwise stated, by the addition of anhydrous magnesium sulfate (Mallinckrodt AR 6070). The drying agent was removed by gravity filtration and was always washed thoroughly with several fresh portions of the solvent.

Melting points observed in sealed tubes were determined using an oil bath and are corrected. All other melting points were observed using a Köfler hot stage and are corrected. Microanalyses were performed by Galbraith Laboratories (Knoxville, Tennessee) and Bernhardt Laboratories (Mülheim, West Germany). A Perkin Elmer Model 137 Infracord recording spectrophotometer was used to determine all infrared spectra. Potassium bromide was used for all pellet spectra. Ultraviolet spectra were determined using a Beckman Model DK-1 recording spectrophotometer. Optical rotations were determined using a Bellingham and Stanley polarimeter (Model No. 397619) equipped with a General Electric Sodium Lab-Arc lamp as the source of the sodium D line. The error given indicates the maximum deviation from the average value for several measurements. Refractive indices were measured using a Bausch and Lomb Abbé-56 refractometer.

Nuclear magnetic resonance (n.m.r.) spectra were determined using a Varian Model A-60 spectrometer. The magnet temperature was essentially constant at some value between 30° and 40° during the determination of a given spectrum. Chemical shift values are reported herein in τ units ($\tau = 10-\delta$). Except as otherwise indicated, tetramethylsilane (TMS) or 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) was used as internal standards. The 500 cps scale width was used for all spectra given as figures, except as otherwise indicated. Unless otherwise indicated, the spectra were calibrated with certain standards to correct for possible scale width deviations (*i.e.*, TMS (10.00 τ) and chloroform (2.75 τ) for the 500 cps scale, acetonitrile (8.03 τ) and cyclohexane (8.56 τ) for the 50 cps scale). Spin-spin coupling constants (*J*, measured in cps) given with more than one significant figure were determined using the 50 cps

scale. Concentrations given for spectra determined using solutions are per cent by weight.

Ozonolyses were performed using a Welsbach Corp. Model T-23 laboratory ozonator as the source of ozone. The rate of production of ozone was determined by reaction with aqueous potassium iodide buffered with potassium hydrogen phthalate followed by titration of the iodine produced with standard aqueous sodium thiosulfate (32).

Gas-liquid chromatography (GLC) was performed using a Glowall Corp. Chromalab Model A-110 instrument equipped with a Minneapolis Honeywell continuous recorder. The columns employed (dimensions 6 ft. x 4 mm.) were packed (all materials were purchased from Applied Science Laboratories) with either 2.8 per cent SE-30 on acid washed, silanized Chromasorb W or 14 per cent ethylene glycol adipate (EGA) on the same support. A given column was always equilibrated for several hours before use at the column temperature (C.T.) and argon inlet pressure (A.I.P.) indicated. The retention time (R.T.) for a given peak was measured from the solvent front (initial recorder response). Peak areas were measured using a Gelman Instruments Co. (Model 39231) planimeter.

Paper chromatography was performed as described previously (33). The solvents used were all redistilled and the systems were prepared no longer than one month before use. The solvent systems that were used and their abbreviations are: t-amyl alcohol:n-propyl alcohol:water, 4:1:1 (v/v) (APW-1) and 4:1:1.5 (v/v) (APW-1.5), n-butyl alcohol:ethanol:water, 4:1:1.5 (v/v) (BEW), t-butyl alcohol:acetic acid:water, 2:1:1 (v/v) (BAW), and ethyl acetate:acetic acid:water, 9:2:2 (v/v) EAW). The spray reagents used, their abbreviations, and the references for their

preparation and interpretation are: aqueous sodium metaperiodate (2%), (SP) (34), aqueous potassium permanganate (1%)-sodium carbonate (2%), (PC) (35), and ninhydrin (N) (36). Thin-layer chromatography (TLC) was performed as described elsewhere (37).

Carbon column chromatography was performed using pretreated Darco G-60 (Atlas Powder Company) and acid-washed Celite (Johns-Manville Corporation) prepared and used as described previously (33).

Silicic Acid chromatography columns were prepared by mixing the indicated amount of silicic acid (100 mesh, Mallinckrodt AR 2847) with chloroform. The slurry was placed in a cylindrical column that had a coarse fritted glass disc at the bottom. The column was packed by draining the excess chloroform, accompanied by stirring, followed by vibration until the adsorbant was firm. The packed dimensions are given in the text.

Qualitative color tests used were: ninhydrin (36), ferric chloride (38), and Benedict's (39).

Ion exchange resins used were regenerated and used as described previously (33). In addition, cation exchange resin Dowex 50W-X8 (100-200 mesh, Baker reagent 1930) was regenerated by stirring with 4 N hydrochloric acid for several hours and washing with distilled water until the washings were free of chlorides (no precipitate with 2% aqueous silver nitrate). The other resins used and their abbreviations are: Amberlite anion exchange resin 45 in the hydroxyl (IRA 45(OH^-)) or the chloride (IRA 45(Cl^-)) phase. Resins were measured for use by allowing them to settle to constant volume in a graduated cylinder. All pH measurements were made using Hydrion paper (Micro Essential Laboratory).

The L-Rhamnose Approach

Attempted Synthesis of L-Streptose

Methyl α- and Methyl β-L-Rhamnopyranoside. A mixture of methyl α- and methyl β-L-rhamnopyranoside was prepared as described elsewhere (40,41). L-Rhamnose hydrate (Matheson Coleman and Bell 5835, 50.35 g., 0.277 mole) and 1.00 l. of anhydrous methanolic hydrogen chloride (1.0%) gave 54.12 g. (110%, contaminated with methanol) of colorless syrup, $[\alpha]_D^{26}$ - 49.7 ± 1.0° (c 11.0, water) [lit. (42) methyl α-L-rhamnopyranoside, m.p. 108-109°, $[\alpha]_D^{20}$ -62.3° (c 0.86, water); lit. (43) methyl β-L-rhamnopyranoside, m.p. 140°, $[\alpha]_D$ +95.2° (water)]. The mixture distilled at 148-160° (0.3-0.5 mm.) [lit. (41), b.p. 145-150°, 0.14 mm.] and gave 35.16 g. (71%) of colorless syrup, $[\alpha]_D^{26}$ -46.7 ± 1.0° (c 10.66, water). Because of the large reduction in yield, the product was not usually distilled before use. GLC (SE-30, A.I.P. 10.0 psig, C.T. 95°) analysis of the undistilled product showed peaks at retention times of 17.29 min. (area 0.44 in.^{2}) and 18.90 min. (area 8.05 in.^{2}). Paper chromatography (APW-1, SP and PC) of the mixture showed only one spot at R_F 0.80 (R_G 4.0).

The n.m.r. spectrum (20%, acetone-D_6) showed absorptions at 8.74 (3H, doublet, J = 6) and 6.68 τ (3H, singlet) and a series of partially resolved overlapping multiplets from 5.36 to 6.56 τ (8H).

Methyl 2,3-O-Isopropylidene-α-L-rhamnopyranoside. A 195.0 g. (1.09 mole) portion of the mixture of methyl α- and methyl β-L-rhamnopyranoside was treated as described elsewhere (40,41). The syrupy product was distilled *in vacuo* using a spinning band distillation column (Nester-Faust Model NF 135). The fraction boiling at 82-93° (0.4-0.6

mm., reflux ratio 5:1) was collected and weighed 92.90 g. (39%). The product showed $[\alpha]_D^{27}$ -24.6 ± 0.5° (c 3.45, dry methanol) and η_D^{20} 1.4550 [lit. (41), b.p. 110-112° (1 mm.), $[\alpha]_D^{24}$ -14.1 (c 1.485, water), η_D^{26} 1.4533; lit. (44), b.p. 104-105° (0.8 mm.) $[\alpha]_D^{24}$ -11.9 (c 3.366, methanol), η_D^{24} 1.4545].

GLC (SE-30, A.I.P. 10 psig, C.T. 95°) analysis of the preparation showed peaks at R.T. 13.78 min. (area 0.06 in.^{2}) and 16.22 min. (area 3.38 in.^{2}). Paper chromatography (APW-1, SP and PC) of the preparation showed only one faint spot at R_F 0.93 (R_G 4.65). The infrared spectrum (liquid film) of the compound showed λ_{max} 2.83, 3.39, 6.89, 7.24, 8.78, 9.16, and 11.64 μ, among others. The n.m.r. spectrum (19%, deuteriochloroform) of the compound showed absorptions at 8.79 (3H, doublet, J = 6.04), 8.71 (3H, singlet), 8.54 (3H, singlet), 6.72 (3H, singlet), 6.61 (1H, quartet, J = 6.07), 6.44 (1H, broad, singlet), 6.15 (1H, doublet, J = 5.97), 6.04 (1H, singlet), 6.01 (1H, doublet, J = 5.92), and 5.30 τ (1H, singlet).

Fractional vacuum distillation using a 6 in. Vigreux column gave higher yields (70%); however, the product showed an intense spot at R_F 0.80 when chromatographed on paper (APW-1, SC and PC).

Methyl 2,3-O-Isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose.

Exploratory oxidations of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside. A number of oxidations of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside were performed using the chromium trioxide-pyridine complex. The effects of varying both the oxidation conditions and the isolation procedure were studied. The results are summarized in Table 1.

The chromium trioxide-pyridine complex was prepared as described

Table 1. Exploratory Oxidations of Methyl 2,3-O-Isopropylidene-α-L-rhamnopyranoside.

Reaction	Conditions[a] R	t	P	Recovery, %[b]	Estimated % Oxidized[c]
1	3	0.1	A	34	6
2	3	0.8	A	26	47
3	3	5	A	21	52
4	3	8	A	18	54
5	10	3	B	47	78
6	10	6	B	28	82
7	10	6	B	50	84
8	10	7	C	40	81
9	10	1	C	66	51
10	10	1	C	16	97
11	10	1	D	94	43
12	10	1	E	98	47
13	10	1	E	78	39
14	10	1	E	68	40

[a] R, ratio of moles of chromium trioxide to moles starting alcohol; t, time in days; P, isolation procedure. All of the reactions were stirred at room temperature except No. 10 which was stirred at 55-60°.

[b] Per cent by weight.

[c] The per cent of the recovery that was oxidized as estimated from the infrared spectra.

elsewhere (45). The complex was always prepared and used as a 10 per cent slurry in anhydrous pyridine. Anhydrous chromium trioxide (Baker reagent 1638) was used. Methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside was always added to the slurry in one portion as a 10 per cent solution in anhydrous pyridine. The reaction was stirred vigorously for the indicated time interval. Several different procedures were used to isolate the product.

For a typical oxidation of 1.0 g. of the starting alcohol, isolation procedure A involved pouring the reaction mixture into 200 ml. of an ice-water mixture. The solution was extracted with three 150-ml. portions of chloroform. The combined chloroform extract was washed with four 100-ml. portions of a mixture of ice and 2 N hydrochloric acid, dried, and evaporated. Procedure B was identical to A except that the acid washings were combined and washed with three 400-ml. portions of chloroform. The chloroform washings were combined with the other chloroform solution.

Procedure C involved the evaporation of the pyridine from the reaction mixture *in vacuo* at temperatures less than 30°. The solid residue was triturated with three 100-ml. portions of chloroform. The extracts were filtered with suction through a Celite mat on sintered glass. The combined extract was washed with two 100-ml. portions of a mixture of ice and 2 N hydrochloric acid. The acid washings were combined and extracted with three 200-ml. portions of chloroform. All chloroform solutions were combined, dried, and evaporated. Procedure D was identical to C except that the pyridine was evaporated *in vacuo* at 45° over a period of about one hour. Procedure E was identical to D except that the time required for the pyridine evaporation was about two hours.

The residue from the evaporation of the chloroform extract was invariably a brown syrup. The extent of oxidation was determined by comparison of the infrared spectrum (liquid film) of the residue with a series of spectra of mixtures of the starting alcohol and the purified ketone.

When the reaction was stirred for longer than one day, the infrared spectrum of the residue indicated the presence of a component with absorption at 5.54 μ. This material was never observed in appreciable amounts (or isolated) in the preparative scale oxidations.

Preparative oxidations of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside. Isolation procedure E was used for all large oxidations (stirred for one day at room temperature). The syrupy residue was immediately* chromatographed on silicic acid that had been equilibrated with water in a closed container for one day.** The column used for 41.728 g. of crude product contained 720 g. of silicic acid and was 38.6 cm. by 6.7 cm. The column was eluted with chloroform (fraction volume 100 ml.). Fractions 1-10 contained 0.668 g. of an unidentified mixture of materials. Fractions 11-21 contained 14.614 g. of the desired product. The infrared spectra (liquid film) of these fractions showed very little absorption in the 2.5-3.1 μ region. GLC (SE-30, A.I.P. 10 psig) analysis of these fractions showed only one peak at column temperatures of 150° (R.T., 1.74 min.) and 95° (R.T., 12.77 min.). Fractions

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* If the syrup was not chromatographed immediately, considerable amounts of other products were obtained as noted in the following section.

** If a freshly opened container of silicic acid was used, the components of the crude product were not separated.

22-41 contained 3.603 g. of mixtures of the desired product and the starting material. Fractions 42-79 contained 17.143 g. of starting material. Further elution (using 10% methanol in chloroform) yielded small amounts of unidentified mixtures. A summary of the results of the large scale oxidations is given in Table 2.

Table 2. Preparative Oxidations of Methyl 2,3-O-Isopropylidene-α-L-rhamnopyranoside.

Reaction	Recovery[a]	Estimated % Oxidized	Yield[a]		
			Product	Reactant	Mixtures
1	66	39	21	39	19
2	67	51	46	36	8
3	68	43	35	41	9
4	83	--	31	48	5

[a] The recovery is per cent by weight. The yields of product, reactant and mixtures of the two are all per cent by weight of the recovered material.

The infrared spectrum (liquid film) of methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose showed λ_{max} 3.40, 5.74, 6.91, 7.25, 8.15, 9.20, 10.21, and 11.66 μ, among others. The compound showed $[\alpha]_D^{27}$ -67.2 ± 0.6° (c 3.08, chloroform). The n.m.r. spectrum (28%, deuteriochloroform) is given as Figure 1.

Identification of maltol as a by-product of the oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside. The crude product of a particular oxidation (one day, isolation procedure E) of methyl 2,3-O-

isopropylidene-α-L-rhamnopyranoside* (106.56 g.) was allowed to stand at room temperature for two weeks before chromatography on silicic acid (1.5 kg., column 79 cm. x 6.4 cm.) using chloroform (fraction volume, 500 ml.). The solvent was evaporated and the infrared spectrum (liquid film) determined for each fraction before combination. Fractions 1-5 contained no material. Fractions 6-21 contained 18.14 g. of syrupy methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose. Fractions 22-46 (eluted with 2% methanol in chloroform) contained 37.85 g. of a mixture of yellow syrup and crystals. The infrared spectra (chloroform solution) of these fractions showed intense absorption at 2.54 and 6.15 μ and moderate absorption at 5.75 μ.** Fractions 47-52 (eluted with 5% methanol in chloroform) contained 3.73 g. of orange syrup. The infrared spectra (liquid film) of these fractions showed intense absorption at ca. 2.95 μ and weak absorption at 5.75 and 6.19 μ. Fractions 53-71 (eluted with 5% methanol in chloroform) contained 28.36 g. of yellow syrupy starting material.

Fraction 22 (5.93 g., yellow syrup and crystals) was triturated with boiling redistilled cyclohexane and filtered. After two recrystallizations from redistilled cyclohexane, the product (0.185 g.) showed m.p. 158.5-161.0° (sealed tube), $[\alpha]_D$ 0 ± 0.3° (c 5.0, methanol). The compound sublimed at 100° at one atmosphere and gave a dark purple-red

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* This particular starting material was contaminated with methyl rhamnopyranoside. Paper chromatography (APW-1, SP and PC) showed an intense spot at R_F 0.80.

** When the infrared spectrum of a recrystallized sample of the solid was obtained, the combined fractions were estimated to contain ca. 60-80% of the compound with absorption at 6.15 μ.

ferric chloride test. The ultraviolet spectrum of the compound in 0.1 N aqueous sodium hydroxide showed λ_{max} 320 ± 2 mμ, ε 5,500 and in 0.1 N hydrochloric acid showed λ_{max} 276 ± 2 mμ, ε 7,390. The infrared spectrum (8%, chloroform, 0.1 mm. path) showed λ_{max} 3.04, 3.31, 6.17, 6.40, 7.93, 8.42, 10.87, and 11.78 μ, among others. The n.m.r. spectrum (saturated deuteriochloroform solution) of the compound showed absorptions at 7.63 (3H, singlet), 3.55 (1H, doublet, J = 5.9), 2.84 (1H, broad, singlet) and 2.33 τ (1H, doublet, J = 5.8).

The above properties are in agreement with those of maltol [lit. (46), m.p. 161-162°, sublimes at 93° (1 atm.), λ_{max} (0.1 N hydrochloric acid) 274 mμ (ε, 8,400), λ_{max} (0.1 N sodium hydroxide) 317 mμ (ε, 7,300)]. The melting point of a portion of the compound thoroughly mixed with a recrystallized sample of maltol (Calbiochem.) was 159.0-161.0° (sealed tube). The infrared and n.m.r. spectra of authentic maltol were identical to those given above.

A small portion of the compound was recrystallized twice from redistilled cyclohexane for elemental analysis. The analytical sample showed m.p. 160-162.5° (sealed tube).

Anal. $C_6H_6O_3$ (126.1) Calc'd: C, 57.14; H, 4.79
Found : C, 57.24; H, 5.71

Another portion of the compound was recrystallized twice and sublimed twice.

Anal. Found : C, 57.50; H, 5.55

Methyl 2,3-O-Isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose Oxime. A solution containing methyl 2,3-O-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose (1.190 g., 5.52 mmole), absolute ethanol (12.0

ml.), hydroxylamine hydrochloride (1.200 g., 17.3 mmole) and anhydrous pyridine (12.0 ml.) was boiled under reflux for two hours. The cooled solution was poured into 100 ml. of a mixture of ice and 2 N hydrochloric acid. The resulting solution was extracted with four 75-ml. portions of chloroform. The combined chloroform extract was washed with two 100-ml. portions of 2 N hydrochloric acid. The combined acid washings were extracted with two 100-ml. portions of chloroform. The chloroform solutions were combined, dried, and evaporated. During the overnight refrigeration, the residue (0.892 g., 70%) crystallized. After recrystallization from redistilled cyclohexane, the colorless crystalline product (0.410 g., 32%) showed m.p. 124.5-126°, $[\alpha]_D^{25}$ -121.7 ± 0.8° (c 20.66, chloroform). The infrared spectrum (pellet) showed λ_{max} 2.94, 3.41, 6.19, 7.04, 8.00, 9.23, 10.52, 11.22, and 12.29 μ, among others. The n.m.r. spectrum (15%, deuteriochloroform, uncalibrated) of the compound showed absorption at 8.63 (3H, singlet), 8.48 (3H, doublet, J = 6.80), 8.43 (3H, singlet), 6.57 (3H, singlet), 5.72 (1H, doublet, J = 7.60), 5.35 (1H, singlet), 5.22 (1H, doublet, J = 7.47), 5.09 (1H, quartet, J = 6.72), and 0.83 τ (1H, broad, singlet).

A small portion of the compound was recrystallized four times from redistilled cyclohexane for elemental analysis. The analytical sample showed m.p. 126.5-128.0°.

Anal. $C_{10}H_{17}NO_5$ (231.3) Calc'd: C, 51.94; H, 7.41; N, 6.06
Found : C, 51.73; H, 7.28; N, 6.11

1-Vinylcyclohexanol. A solution containing 0.118 mole (assayed by the volumetric determination of the ethylene produced upon decomposition with water) of vinylmagnesium chloride in tetrahydrofuran (solution

purchased from Columbia Organic Chemicals, Inc.) was added dropwise with stirring to 5.25 ml. (5.0 g., 50.8 mmole) of redistilled cyclohexanone dissolved in 30 ml. of anhydrous benzene. The solution was boiled under reflux for two hours and then allowed to stand at room temperature overnight. The solution was diluted with 50 ml. of anhydrous benzene and added to 50 ml. of an ice-water mixture that contained 1.0 g. of ammonium chloride. The resulting emulsion was extracted with three 500-ml. portions of ether. The extracts were combined, dried, and evaporated. The residue (6.06 g., 95%) was distilled *in vacuo*. The portion (1.666 g., 26%) boiling at 50-55° (1 mm.) [lit. (47), b.p. 66-68° (14 mm.)] was collected. The infrared spectrum (liquid film) of the compound showed λ_{max} 2.92, 3.41, 6.09, 6.91, 7.93, 9.43, and 10.42 μ, among others. The n.m.r. spectrum (neat liquid, uncalibrated) of the compound showed absorption at 8.47 (10H, singlet), 4.13 (1H, singlet), and a series of peaks from 3.73 to 5.12 τ (3H).

Methyl 2,3-O-Isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside. A mixture of anhydrous tetrahydrofuran (25 ml.) and clean magnesium turnings (3.017 g., 0.124 mole) was placed in a 200-ml. three-neck flask equipped with a stirring motor, an addition funnel, and a dry ice-acetone condenser. The system was periodically flushed with dry nitrogen during the following manipulations. Vinyl bromide (1.5 ml.) was added. After the initial vigorous reaction had subsided, an additional 15.0 ml. (total 25.1 g., 0.23 mole) of vinyl bromide dissolved in 60 ml. of anhydrous tetrahydrofuran was added at a rate that maintained a moderate reflux. The brown mixture was stirred until all of the magnesium had reacted (30 min.). A solution of freshly prepared methyl 2,3-O-isopropylidene-6-

deoxy-α-L-lyxo-hexopyranos-4-ulose (3.258 g., 15.1 mmole) in anhydrous tetrahydrofuran (30 ml.) was added dropwise at a rate that maintained a moderate reflux. The dry ice-acetone condenser was replaced by an efficient cold water condenser and the solution was boiled under reflux for one hour. The cooled solution was stirred at room temperature overnight in the dark. The mixture (white precipitate) was slowly poured with stirring into 100 ml. of an ice-water* mixture (foaming and vigorous boiling occurred). The resulting emulsion was extracted with four 800-ml. portions of ether. The extracts were combined, dried, and evaporated. The yellow syrupy residue (3.853 g., 104%) was chromatographed using silicic acid (80.0 g., column 16.8 cm. x 3.6 cm.) and chloroform (fraction volume, 50 ml.). Fractions 1-3 contained no material. Fractions 4-12 contained 2.043 g. (55%) of crystalline product, m.p. 39-44°. Fractions 13-25 contained 0.464 g. (13%) of colorless syrupy material (the infrared spectra of these fractions were almost identical to that of the crystalline material). Fractions 26-67 (eluted with 5% methanol in chloroform) contained 1.104 g. of yellow-orange material (the infrared and n.m.r. spectra of this material were poorly defined).

Fractions 4-12 were combined and sublimed (25-33°, 0.035 mm.) and yielded 1.798 g. (49%) of material, m.p. 38-46°.

A small portion of the compound was sublimed twice for elemental analysis. The analytical sample showed m.p. 44.5-46.5°, $[\alpha]_D^{27}$ -21.7 ± 1.2° (c 3.96, chloroform).

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* If 0.1 N hydrochloric acid or saturated aqueous ammonium chloride was used, very little product was obtained.

Anal. $C_{12}H_{20}O_5$ (244.3) Calc'd: C, 59.00; H, 8.25
Found : C, 59.14; H, 8.29

The infrared spectrum (pellet) of the compound showed λ_{max} 2.73, 3.37, 6.10, 7.24, 8.24, 9.19, 10.82, and 11.70 μ, among others. The n.m.r. spectrum (16%, deuteriochloroform) of the compound is given as Figure 2.

GLC (SE-30, A.I.P. 10 psig, C.T. 100°) analysis of the product before chromatography showed peaks with R.T. 0.83-9.59 (nine small peaks, total area 0.46 in.^{2}), 11.64 (area 0.22 in.^{2}), 18.32 (area 0.47 in.^{2}), 20.81 (area 2.79 in.^{2}), and 27.90 min. (area 0.24 in.^{2}). After chromatography and one sublimation, GLC (same conditions) of the product showed only one peak (R.T. 21.48 min.). Based on these data, the crude product contained 66.5 per cent of the desired compound.

The Stability of 1-Vinylcyclohexanol to Acid.

Hydrolysis of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside. The hydrolysis of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside to methyl α-L-rhamnopyranoside and finally L-rhamnose, was investigated using 1 N hydrochloric acid at room temperature and 50-55° and using Dowex 50W-X8 (H^+). The course of the hydrolysis was followed by paper chromatography (APW-1, SP and PC) of small portions of the reactions, withdrawn twice daily. Paper chromatography of methyl α-L-rhamnopyranoside (R_F 0.80) and L-rhamnose (R_F 0.47) were used as standards for the identification of the hydrolysis products.

A solution of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (65.7 mg.) in 1 N hydrochloric acid (1.32 g.) was allowed to stand at room temperature. An intense spot at R_F 0.8 was present after 2.5 hr.

After seven days, two spots of about equal intensity were observed at R_F 0.4 and 0.8.

A solution of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (53.2 mg.) in 1 N hydrochloric acid was maintained at 50-55°. After 19 hr., two spots of about equal intensity were observed at R_F 0.4 and 0.8. After 115 hr. only one spot was present (R_F 0.4).

A mixture of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (331 mg.), redistilled dioxane (4 ml.), water (2 ml.) and Dowex 50W-X8 (H^+) (0.3 ml.) was shaken at room temperature. After 13 days, the spot at R_F 0.8 was about twice as intense as the spot at R_F 0.4.

Stability of 1-vinylcyclohexanol to acid. A solution of 1-vinylcyclohexanol (0.50 g.), acetone (3 ml.) and 1 N hydrochloric acid (1 ml.) was allowed to stand at room temperature for 48 hr. The solution was diluted with acetone and water and sodium bicarbonate (7 g.) was added. The solution was extracted with two 30-ml. portions of chloroform. The combined extract was dried and evaporated. The n.m.r. spectrum (10%, carbon tetrachloride) of the residue (0.43 g.) showed absorption at 7.3-9.2 τ (broad, partially resolved peaks). Very little absorption was present in the rest of the spectrum.

A solution of 1-vinylcyclohexanol (0.50 g.), acetone (3 ml.) and 1 N hydrochloric acid (1 ml.) was maintained at 50-55° for 48 hr. The product was isolated as described above. The n.m.r. spectrum (10%, carbon tetrachloride) of the residue (0.31 g.) showed broad partially resolved absorption at 7.4-9.2, 6.2-6.7 and 4.0-5.4 τ.

A mixture of 1-vinylcyclohexanol (287 mg.), redistilled dioxane (4 ml.), water (2 ml.) and Dowex 50W-X8 (H^+) (0.3 ml.) was shaken

vigorously for 48 hr. The resin was removed by decantation and was washed well with dioxane and water. The supernatant was evaporated. A solution of the residue in chloroform was dried and evaporated. The n.m.r. spectrum (10%, carbon tetrachloride) of the residue (210 mg.) showed broad, partially resolved absorption at 7.3-9.1 and 4.2-5.7 τ.

Ozonolysis of Methyl 2,3-O-Isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside. A mixture of ozone and oxygen was bubbled through a solution containing methyl 2,3-O-isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside (1.250 g., 5.13 mmole), anhydrous pyridine (0.43 g., 5.45 mmole), and redistilled methylene chloride (70.0 ml.), at -81° for 14.4 min. (10.2 mmole of ozone). The solution was poured onto zinc powder (6.54 g.) in a water bath at 25°. The mixture was stirred at 25° for two hours. After filtration, the solution was washed with 2 N hydrochloric acid (30 ml.) and saturated aqueous sodium bicarbonate. The acid washing was extracted with two 30-ml. portions of methylene chloride. All methylene chloride solutions were combined, dried, and evaporated. The residue (0.728 g., 58%) was a yellow syrup that resisted crystallization. The infrared spectrum (liquid film) of the residue showed λ_{max} 2.76, 3.37, 5.77 (sharp, intense), 7.25, 8.24, 9.16, 11.78, and 13.21 μ, among others. The n.m.r. spectrum (30%, carbon tetrachloride) of the residue showed absorption at 8.93 (3H, doublet, J = 7), 8.74 (3H, singlet), 8.51 (3H, singlet), 6.70 (3H, singlet), 6.67 (1H, broad, singlet), 6.29 (1H, quartet, J = 7), 6.02 (1H, doublet, J = 7), 5.63 (1H, doublet, J = 7), 5.20 (1H, singlet), and 0.44 τ (1H, singlet).

After chromatography of the residue using silicic acid and chloroform, the n.m.r. and infrared spectra were changed. The presence of

absorptions other than those described indicated that the product decomposed during chromatography.

Attempted Oxidations of Methyl 2,3-O-Isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside. A solution containing methyl 2,3-O-isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside (0.249 g., 1.20 mmole), distilled water (35 ml.) and potassium permanganate (0.666 g., 4.22 mmole) was warmed on the steam bath for 30 min. The mixture (pH 9) was filtered and washed with four 50-ml. portions of chloroform. The washings were combined, dried, and evaporated and yielded 49 mg. of orange syrup. The aqueous solution was acidified (pH 2.5) and extracted with four 50-ml. portions of chloroform. The combined extract was dried, evaporated, and yielded 31 mg. of brown syrup.

A solution of methyl 2,3-O-isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside (0.335 g., 1.37 mmole) in distilled water (25 ml.) was added to 160 ml. of 0.029 M aqueous silver permanganate (4.67 mmole). The solution was allowed to stand at room temperature for 22 hr. The mixture was treated as described above and yielded 28.2 mg. of neutral material (yellow syrup) and 27 mg. of acidic material (orange syrup).

Synthesis of 4-Amino-4,6-dideoxy-L-talose Hydrochloride

Methyl 2,3-O-Isopropylidene-4-O-(p-toluenesulfonyl)-α-L-rhamnopyranoside. A solution of p-toluenesulfonyl chloride (57.30 g., 0.301 mole) in anhydrous pyridine (100 ml.) was added dropwise with swirling and cooling (0-3°) to a solution of the mixture of methyl 2,3-O-isopropylidene-α- and methyl 2,3-O-isopropylidene-β-L-rhamnopyranoside in anhydrous pyridine (100 ml.). After the addition was complete (20 min.), the solution was allowed to stand in a melting ice bath for two hours and then

was maintained at 60° overnight. The black solution was added to 250 ml. of an ice-water mixture and the resulting mixture was extracted with four 250-ml. portions of chloroform. The combined extract was washed with three 500-ml. portions of both 2 N hydrochloric acid and five per cent sodium bicarbonate solution. The extract was dried and evaporated. The orange residue was dissolved in ethanol (200 ml.) and decolorized with Darco G-60 (4.0 g.). After filtration and evaporation there was obtained 36.277 g. (93%) of yellow syrup. During storage in the refrigerator for one month, the product crystallized. After recrystallization from redistilled petroleum ether (b.p. 30-60°), there was obtained 23.090 g. (59%) of colorless methyl 2,3-O-isopropylidene-4-O-(p-toluenesulfonyl)-α-L-rhamnopyranoside, m.p. 59.5-61.5°, $[\alpha]_D^{27}$ +21.2 ± 0.8° (c 3.68, methanol) [lit. (40), m.p. 60°, $[\alpha]_D^{15}$ +22.5° (c 2.9, methanol), lit. (44), m.p. 61-62°, $[\alpha]_D^{24}$ +21.94° (c 3.030, methanol)]. The infrared spectrum (pellet) of the compound showed λ_{max} 3.30, 6.26, 6.91, 7.38, 8.51, 9.13, 10.23, 11.51, and 12.89 μ, among others. The n.m.r. spectrum (19%, carbon tetrachloride, uncalibrated) of the compound showed absorption at 8.81 (3H, singlet), 8.72 (3H, doublet, J = 7), 8.58 (3H, singlet), 7.59 (3H, singlet), 6.71 (3H, singlet), 5.94-6.49 (4H, partially resolved multiplets), 5.28 (1H, singlet), 2.78 (2H, doublet, J = 10), and 2.26 τ (2H, doublet, J = 10). GLC (SE-30, A.I.P. 10 psig, C.T. 170°) analysis of the compound showed one peak (R.T. 42.80 min.).

Methyl 2,3-O-Isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranoside Hydrochloride. A solution of methyl 2,3-O-isopropylidene-4-O-(p-toluenesulfonyl)-α-L-rhamnopyranoside (19.151 g., 51.3 mmole), sodium azide (4.827 g., 74.3 mmole), distilled water (40 ml.) and redistilled

dimethyl formamide (1.00 l.) was boiled under reflux for 21 hr. The solution was cooled to 10° and added to a mixture of 1.50 l. of saturated sodium chloride solution and 250 g. of ice. The resulting solution was extracted with four 1.0-l. portions of ether. The combined extract was washed with five 250-ml. portions of saturated aqueous sodium chloride, dried, and evaporated. The infrared spectrum (liquid film) of the residue showed intense absorption at 5.97 μ. To remove the residual dimethyl formamide, a solution of the residue in 150 ml. of ether was washed with five 25-ml. portions of saturated aqueous sodium chloride, dried, and evaporated. The infrared spectrum (liquid film) of the yellow syrupy residue (10.256 g., 82%) showed absorption at 3.38, 4.72, 6.87, 7.24, 9.14, 10.52, and 11.52 μ, among others. No appreciable absorption was observed in the 5.5-6.7 μ region.

A solution of the syrupy methyl 2,3-O-isopropylidene-4-azido-4,6-dideoxy-α-L-talopyranoside (10.256 g., 41.2 mmole) in anhydrous ether (25 ml.) was added dropwise with stirring to a solution of lithium aluminum hydride (7.20 g., 0.190 mole) in anhydrous ether (500 ml.). The mixture was boiled under reflux for seven hours. The excess hydride was destroyed by the addition of wet ether and then water. The aqueous layer was separated and extracted with three 300-ml. portions of ether. The combined ethereal solution was washed with two 150-ml. portions of saturated aqueous sodium chloride, dried and concentrated to 250 ml. Anhydrous hydrogen chloride was passed through the solution for 15 min. The white precipitate that resulted was filtered, washed with dry ether, and immediately dried *in vacuo* at room temperature. The hygroscopic cream-colored product weighed 3.560 g. (34%), m.p. 171-180°, and gave a purple

ninhydrin test. After recrystallization from n-butyl ether, the hygroscopic white crystalline methyl 2,3-O-isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranoside hydrochloride (2.408 g., 23%) showed m.p. 176.5-180° and $[\alpha]_D^{27}$ -30.2 ± 0.7° (c 4.12, anhydrous methanol). The infrared spectrum (pellet) of the product showed λ_{max} 2.82, 3.21, 3.32, 6.78, 7.26, 8.25, 8.65, 9.10, 9.38, 10.52, 11.60, 12.12, and 12.79 μ, among others. The n.m.r. spectrum (24%, deuterium oxide) is given as Figure 3.

A small portion of the compound was recrystallized from n-butyl ether twice for elemental analysis. The analytical sample showed m.p. 175.5-181°.

Anal. $C_{10}H_{20}NO_4Cl$ (253.7) Calc'd: C, 47.34; H, 7.95; N, 5.52; Cl, 13.97
Found : C, 47.02; H, 7.92; N, 5.27; Cl, 13.96

Paper chromatography of the compound using APW-1.5 (N) showed an intense purple spot at R_F 0.55. If an aqueous solution of the compound was allowed to stand at room temperature for several weeks before chromatography, two other spots were present at R_F 0.10 (faint pink-purple) and 0.18 (moderate, purple).

Methyl 2,3-O-Isopropylidene-4-(3,5-dinitrobenzamido)-4,6-dideoxy-α-L-talopyranoside. 3,5-Dinitrobenzoyl chloride (0.418 g., 1.81 mmole, recrystallized, m.p. 66-68°) was added in small portions with swirling to a solution of methyl 2,3-O-isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranoside hydrochloride, anhydrous pyridine (5 ml.) and anhydrous benzene (10 ml.). The resulting mixture was maintained at 65-80° in a water bath for 45 min. The solution was cooled to room temperature; distilled water (25 ml.) and saturated aqueous sodium bicarbonate (15 ml.)

were added. The mixture was stirred at room temperature for 45 min. The aqueous layer was removed and extracted with four 10-ml. portions of benzene. The benzene solutions were combined, dried, and evaporated. The syrupy residue (0.294 g., 90%) was chromatographed using silicic acid (14 g., column 7.6 cm. x 2.3 cm.) and chloroform (fraction volume, 15 ml.). Fractions 1-6 contained no material. Fractions 7-10 contained 0.290 g. (89%) of the semi-crystalline product. After recrystallization from ligroine (b.p. 100-110°), the product (0.174 g., 53%) showed m.p. 121.5-122.5° and $[\alpha]_D^{23}$ -40.3 ± 0.5° (c 4.03, chloroform). The infrared spectrum (pellet) of the product showed λ_{max} 2.91, 3.36, 5.99, 6.46, 7.46, 9.21, and 13.90 μ, among others. The n.m.r. spectrum (21%, deuteriochloroform) of the compound is shown as Figure 4.

A small portion of the compound was recrystallized twice from ligroine (b.p. 100-110°) for elemental analysis. The analytical sample showed m.p. 122.5-123.0°.

Anal.	$C_{17}H_{21}N_3O_9$	Calc'd:	C, 49.64; H, 5.15; N, 10.21
	(411.4)	Found :	C, 49.67; H, 4.97; N, 10.02

Methyl 2,3-O-Isopropylidene-4-acetamido-4,6-dideoxy-α-L-talopyranoside. A solution of anhydrous acetic anhydride (0.50 ml., 0.46 g., 4.5 mmole) and anhydrous pyridine (5.0 ml.) was added slowly to a cooled (0-3°) solution of methyl 2,3-O-isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranoside hydrochloride (0.302 g., 1.19 mmole) in anhydrous pyridine (5.0 ml.). The colorless solution was allowed to stand at room temperature overnight. The solution was poured into 50 ml. of an ice-water mixture and extracted with four 75-ml. portions of chloroform. The combined extract was washed with two 100-ml. portions of 2 N hydrochloric

acid. The combined washings were extracted with three 100-ml. portions of chloroform. The chloroform solutions were combined, dried, and evaporated. The yellow syrupy residue (0.295 g., 96%) was chromatographed on silicic acid (4.0 g., column 7.7 cm. x 1.1 cm.) using chloroform (fraction volume, 5 ml.). Fraction one contained no material. Fractions 2-9 contained 0.265 g. (86%) of colorless syrupy product, $[\alpha]_D^{24}$ -73.3 ± 0.3° (c 10.63, chloroform). The product resisted crystallization. The infrared spectrum (liquid film) of the compound showed λ_{max} 2.99, 3.39, 6.04, 6.48, 7.31, 8.28, 9.18, and 11.52 μ, among others. The n.m.r. spectrum (11%, deuteriochloroform) of the compound showed absorption at 8.83 (3H, doublet, J = 7), 8.70 (3H, singlet), 8.54 (3H, singlet), 8.06 (3H, singlet), 6.54 (3H, singlet), 5.34-5.98 (4H, broad, partially resolved multiplets), 4.99 (1H, singlet), and 3.29 τ (1H, broad, doublet, J = 9).

4-Amino-4,6-dideoxy-L-talose Hydrochloride.

Hydrolysis of methyl 2,3-O-isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranoside hydrochloride. A solution of methyl 2,3-O-isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranoside hydrochloride (0.304 g., 1.20 mmole) in 1 N hydrochloric acid (20 ml.) was maintained at 50-60° for 42.5 hr. After cooling, 45 ml. of IRA 45(OH^-) was added and the mixture was swirled until the pH was 5.5. The resin was filtered and the filtrate was passed directly through a column containing 35 ml. of IRA 45(Cl^-). The resin was washed with distilled water and the washings were passed through the column until the eluent was ninhydrin negative. The total eluent was evaporated and absolute ethanol was evaporated from the residue. After drying in vacuo, the brown semi-solid residue (0.172 g.) was chromatographed using carbon-celite (20.0 g., column 31.7 cm. x 1.6 cm., flow

rate 3.5 ml./hr.). The column was eluted with distilled water (fraction volume, 7 ml.). The fractions were combined as indicated and evaporated to ca. 10 ml. and lyopholized after a drop was tested with ninhydrin reagent. Fractions 1-7 were ninhydrin negative and contained 10.8 mg. of white solid (column throw). Fractions 8-9 were ninhydrin positive (purple) and together contained 42.6 mg. of orange semi-solid. Fractions 10-15 were ninhydrin positive (purple) and contained 36.6 mg. of orange semi-solid. Fractions 16-20 were ninhydrin positive (purple) and contained 8.2 mg. of orange semi-solid. Fractions 21-72 were ninhydrin negative and contained 13.2 mg. of orange semi-solid. The ninhydrin positive fractions were chromatographed on paper (APW-1.5, N). Fractions 8-9 showed spots at R_F 0.15 (yellow), 0.20 (purple), and 0.32 (purple). Fractions 10 and 11 showed spots at R_F 0.09 (pink-purple), 0.20 (purple), and 0.32 (purple). Fractions 12-20 showed a spot at R_F 0.07 (yellow) and faint purple streaking at R_F 0.1-0.3.

Paper chromatography of fractions 8 and 9 using BAW (N) showed spots at R_F 0.38 (yellow), 0.52 (purple), and 0.66 (pink-purple).

Hydrolysis of methyl 2,3-O-isopropylidene-4-acetamido-4,6-dideoxy-α-L-talopyranoside. A solution of methyl 2,3-O-isopropylidene-4-acetamido-4,6-dideoxy-α-L-talopyranoside (2.007 g., 7.76 mmole) in 2.5 N hydrochloric acid (50.0 ml.) was maintained at 100° for six hours. The pH of the cooled solution was adjusted to 3 with IRA 45(OH^-). The resin was filtered and washed thoroughly with distilled water. The solution was concentrated to ca. 15 ml. and chromatographed on Dowex 50W-X8 (H^+) (column 109.0 cm. x 1.40 cm., flow rate 1 ml./min.). The column was eluted with distilled water (1,020 ml.) to remove any neutral material.

The washings were concentrated and lyopholized and yielded 217 mg. of black tar. The column was next eluted with 0.30 N hydrochloric acid (fraction volume 50 ml.). Each fraction was treated with IRA 45(OH^-) batchwise and after the pH was 5.5, was passed directly over an IRA 45(Cl^-) column (volume 15 ml.). The columns were washed with 60 ml. of distilled water and the eluent was concentrated to ca. 10 ml. Paper chromatography (APW-1, SP and PC) of the fractions was investigated. Fractions 1-19 showed a faint spot at the origin. Fractions 20-25 showed an intense spot at R_F 0.10-0.15 together with a faint spot at the origin. Fractions 26-59 showed only a faint spot at the origin.

A few drops of each fraction were tested with Benedict's reagent before the fractions were lyopholized. Fractions 1-19 gave a negative Benedict's test and contained a total of 0.556 mg. of yellow syrup. Fractions 20-25 gave positive Benedict's tests and contained a total of 0.307 mg. of a mixture of crystals and orange syrup. Fractions 26-59 gave negative Benedict's tests and contained a total of 0.578 mg. of yellow syrup.

The product (fractions 20-25) could not be crystallized from water-methanol-ether, water-ethanol-isopropyl ether, methanol-isopropyl ether, or ethanol-isopropyl ether even on prolonged (1-2 months) cooling in the refrigerator. The product oiled out of methanol-ether-petroleum ether (b.p. 30-60°) and from ethanol-ether-petroleum ether (b.p. 30-60°). After prolonged cooling (4 months) in the refrigerator in water-ethanol-isopropyl ether, the sample gave a negative Benedict's test.

The 5-Deoxy-L-arabinose Approach

Synthesis of 1,2-O-Isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose

L-Rhamnose Diethyl Dithioacetal. A modification of the method of Fischer (48) was used to prepare L-rhamnose diethyl dithioacetal. L-Rhamnose hydrate (182.00 g., 1.0 mole) was dissolved in 154 ml. of 12 N hydrochloric acid. The solution was stirred and cooled in an ice bath. Ethanethiol (185 ml., 2.5 mole) was added in a slow continuous stream. The product began to precipitate in large amounts after the addition was about one-half completed. At this time the rate of addition of the ethanethiol and the rate of stirring were increased. The total time required for the addition was 30 min. The reaction mixture was stirred vigorously for 10-15 min. after the addition was completed. Cold water (200 ml., 0°) was added and the product was filtered with suction. The crystalline L-rhamnose diethyl dithioacetal was washed with ether and recrystallized from distilled water. The crystals were dried *in vacuo* for several hours. There was obtained 139.5 g. (52%) of white crystals, m.p. 136.5-139°, $[\alpha]_D^{27}$ -10.1° ± 1.0° (c 2.17, methanol) [lit. (49) m.p. 136-137°, $[\alpha]_D^{25}$ -12.4° (c 2.18, methanol)]. Concentration of the mother liquors yielded an additional 22.3 g. (0.08 mole), m.p. 136-138°. The total yield was 161.8 g. (60%).

1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose. An aqueous solution of peroxypropionic acid was prepared as described elsewhere (50). Propionic anhydride (504 ml.) and 840 ml. of 30 per cent aqueous hydrogen peroxide yielded about 900 ml. of aqueous 4 M peroxypropionic acid. The peracid solution did not decolorize two per cent aqueous potassium permanganate rapidly [a negative test for hydrogen peroxide (51)] and was

used within one week after preparation. The peracid solution was standardized as described elsewhere (52) immediately prior to use.

L-Rhamnose diethyl dithioacetal (54.00 g., 0.200 mole) was dissolved in 210 ml. of p-dioxane (Eastman 2144) with warming. The solution was cooled in an ice bath with stirring. As crystallization began, 320 ml. of 3.78 M peroxypropionic acid (1.21 mmole) was added as rapidly as possible (5 min.) without allowing the vigorous exothermic reaction to become unmanageable. After the addition was complete, the solution was stirred in the ice bath for 10 min. and then allowed to stand in the melting ice bath for one hour. The solution was diluted with 300 ml. of methanol. During concentration of the solution to 300 ml., the product crystallized. The white crystals were filtered with suction and washed thoroughly with cold methanol and cold ether. The product was dried in vacuo at room temperature and weighed 32.30 g., m.p. 105-131°, $[\alpha]_D^{27}$ +5.8 ± 0.5° (c 4.12, methanol)* [lit. (53), 1-deoxy-1, 1-bis(ethanesulfonyl)-L-rhamnose, m.p. 178-180°, $[\alpha]_D$ +7.4° (c 4.06, methanol); 1,1-bis(ethanesulfonyl)-L-arabino-trihydroxyhex-1-ene, m.p. 105-107°, $[\alpha]_D$ -40.2° (c 4.87, methanol)]. The filtrate was diluted with 200 ml. of methanol. Concentration of the solution yielded an additional 13.25 g., m.p. 130-156°. The filtrate was diluted with 300 ml. of ether and the resulting solution yielded 3.30 g., m.p. 102-138°, of crystals after standing overnight in the refrigerator. All portions of the white crystalline product were combined (total weight 48.85 g.) and used without further purification.

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* This material was prepared several times in this manner and the observed physical constants were not reproducible. Melting points of 96-124° and 169-175° were observed. Another sample showed $[\alpha]_D^{27}$ -24.1 ± 0.5° (c 4.12, methanol).

A 113.00 g. portion of the mixture of products from the peracid oxidation was dissolved, with warming, in 700 ml. of distilled water. After the colorless solution was cooled, aqueous ammonia (15 N) was added dropwise until the solution had pH 9. After a few hours standing, bis(ethanesulfonyl)methane began to crystallize on the walls of the flask and the solution became orange. The reaction was allowed to stand at room temperature for three days. The crystalline bis(ethanesulfonyl)methane was filtered with suction. After drying *in vacuo* the crystals weighed 53.05 g., m.p. 101.5-102.5° [lit. (54), m.p. 101-102°]. The filtrate was extracted with four 400-ml. portions of chloroform. After combination, the extracts were dried and evaporated. The residue was an additional 11.33 g. of bis(ethanesulfonyl)methane (total yield, *ca.* 95%). The aqueous solution was evaporated and dried *in vacuo* at room temperature overnight. The resulting orange syrupy 5-deoxy-L-arabinose was dissolved in 200 ml. of anhydrous acetone. After anhydrous magnesium sulfate (20 g.) and Darco G-60 (5 g.) were added, the mixture was allowed to stand overnight. The solids were filtered by gravity and washed with dry acetone. Anhydrous copper sulfate (30 g.) was added and the resulting mixture was again allowed to stand overnight. The copper sulfate was filtered with suction. The yellow filtrate was diluted with 400 m. of anhydrous acetone. Anhydrous copper sulfate (90 g., dried at 150° for one week) and 15 drops of 98 per cent sulfuric acid were added to the solution. The resulting mixture was stirred at room temperature for 24 hr. After the addition of 10.0 g. of anhydrous calcium oxide, the mixture was stirred for an additional hour. The solids were filtered with suction and washed thoroughly with anhydrous acetone. The filtrate and washings were

combined and evaporated. The product (49.74 g.) was a viscous orange syrup that partially solidified after two days in the refrigerator. This material was triturated with six 500-ml. portions of boiling anhydrous ether. The syrupy ether-insoluble residue was set aside. After combination, the ether extracts were evaporated, and gave a solid mass of yellow crystals. This residue was triturated with three 250-ml. portions of hot petroleum ether (b.p. 100-110°). After decantation, each extract was allowed to cool very slowly to room temperature and then was cooled in the refrigerator overnight. 1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose crystallized as cream colored spars. The product was collected and dried. The total yield from all extracts was 18.295 g., m.p. 84.5-86°, $[\alpha]_D^{28}$ -12.7 ± 1.0° (c 6.28, water) [lit. (55), m.p. 83-84°, $[\alpha]_D^{26}$ -13.9 (c 2.006, water), lit. (56), m.p. 82-83°, $[\alpha]_D^{23}$ -13.12° (c 3.201, water)].

Further concentration of the filtrates gave, on cooling, a mixture of syrup and crystals. This material was not collected but was retained as the solvent was evaporated. The residue was combined with the ether-insoluble residue that had been set aside. The total residue weight was 28.60 g. The residue was subjected to the same acetonation conditions (using proportional amounts of reagents) and purification procedure as were used with 5-deoxy-L-arabinose. The yield was 6.717 g., m.p. 84-86°. The insoluble syrupy residue from this procedure was also reacted in a similar manner. The yield was 7.564 g., m.p. 83.5-86°. The syrupy residue (11.23 g.) from the third reaction was chromatographed using chloroform and silicic acid (100 g., column 11.8 cm. x 4.7 cm.). The first fraction (200 ml.) contained 0.703 g. of an unidentified mobile liquid.

The second fraction (1,020 ml.) contained 3.866 g. of crystalline product. The third fraction (500 ml.) contained 0.216 g. of an unidentified orange syrup. Elution of the column with 250 ml. of methanol-chloroform (1:1) yielded 5.536 g. of an orange syrup that gave a positive Benedict's test.

The total yield of crystalline 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose was 36.442 g. (45.4% overall yield from L-rhamnose diethyl dithioacetal).

If the residue from only one acetonation reaction was chromatographed, the yield was less. Silicic acid chromatography of 19.359 g. of crude reaction product yielded 7.186 g. of crystalline 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose and 10.425 g. of recovered orange syrupy 5-deoxy-L-arabinose.

1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose sublimed readily at 50-80° and 0.5 mm. Hg.

Further purification of the compound was best achieved by recrystallization from petroleum ether (b.p. 100-110°). A small sample recrystallized twice, showed m.p. 84.5-85.5° (unchanged by further recrystallization), $[\alpha]_D^{26}$ -16.1 ± 0.6° (c 3.30, water). The infrared sspectrum (pellet) of the compound showed λ_{max} 2.87, 3.32, 6.90, 7.32, 8.25, 9.12, 10.15, and 12.10 μ, among others. The n.m.r. spectrum (19%, deuteriochloroform) is given as Figure 5.

GLC (SE-30, A.I.P. 10 psig, C.T. 100°) analysis of the unrecrystallized compound showed only one peak (R.T. 5.66 min.).

1,2-O-Isopropylidene-3-O-benzoyl-5-deoxy-β-L-arabinofuranose. 1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose (2.20 g., 12.6 mmole) was

dissolved in 6 ml. of anhydrous pyridine. The solution was cooled in an ice bath during the addition of 2.0 ml. (17.3 mmole) of benzoyl chloride. The resulting solution was heated on a steam bath for 30 min. and was poured into 50 ml. of a mixture of ice and water. The resulting mixture was extracted with two 75-ml. portions of chloroform. The extracts were combined and washed successively with two 50-ml. portions of saturated aqueous sodium bicarbonate and two 100-ml. portions of a mixture of ice and 3 N hydrochloric acid. The solution was dried and evaporated. The colorless syrupy residue weighed 2.177 g. To remove residual benzoyl chloride (indicated by absorption at 5.57 μ in the infrared spectrum (liquid film) of the residue), the residue was dissolved in 50 ml. of saturated aqueous sodium bicarbonate. The solution was allowed to stand at room temperature for one day. The extraction procedure used above was repeated. The residue was a viscous yellow syrup (1.522 g., 43%). This material was chromatographed on silicic acid (20.0 g., column 9.5 cm. x 2.3 cm.). The column was eluted with chloroform. Fraction one (75 ml.) contained no material. Fraction two (75 ml.) contained 0.348 g. of colorless syrup. Fraction three (200 ml.) contained 0.666 g. of colorless syrup. Fraction four (eluted with 175 ml. of 5% methanol in chloroform) contained 0.249 g. of yellow syrup. The total yield of 1,2-O-isopropylidene-3-O-benzoyl-5-deoxy-β-L-arabinofuranose was 1.014 g. (29%), $[\alpha]_D^{27}$ +30.2 ± 0.9° (c 7.31, chloroform). The product resisted crystallization. The infrared spectrum (liquid film) of the compound showed λ_{max} 3.33, 5.82, 6.90, 7.91, 9.01, and 14.06 μ, among others. The n.m.r. spectrum (20%, carbon tetrachloride) of the compound is given as Figure 6.

1,2-O-Isopropylidene-3-O-(3,5-dinitrobenzoyl)-5-deoxy-β-L-arabinofuranose. 1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose (0.4585 g., 2.79 mmole) was dissolved in 5 ml. of anhydrous pyridine. 3,5-Dinitrobenzoyl chloride (1.5001 g., 6.53 mmole) was added in small portions with stirring. After the addition was complete, the solution was boiled for five minutes. The hot solution was poured into 25 ml. of ice and water. Saturated aqueous sodium bicarbonate (25 ml.) was added. The resulting mixture was allowed to stand at room temperature for two hours. The mixture was extracted with three 50-ml. portions of chloroform. The extracts were combined and washed with two 100-ml. portions of a mixture of ice and 2 N hydrochloric acid. The solution was dried and evaporated. The semi-solid residue (0.8814 g., 86%) was chromatographed over silicic acid (12 g., column 6.4 cm. x 2.3 cm.) using chloroform. Fraction one (50 ml., 0.00 g.) was discarded. Fraction two (125 ml.) contained 0.5624 g. of crystalline product. Fraction three (eluted with 200 ml. of 10% methanol in chloroform) contained 0.2531 g. of an orange syrup. Recrystallization of fraction two (from 80% ethanol) yielded 0.4341 g. (42%) of crystalline 1,2-O-isopropylidene-3-O-(3,5-dinitrobenzoyl)-5-deoxy-β-L-arabinofuranose, m.p. 114-115°, $[\alpha]_D^{27}$ +29.7 ± 1.0° (c 2.05, chloroform). The infrared spectrum (pellet) of the compound showed λ_{max} 3.36, 5.81, 6.48, 7.44, 8.63, 9.32, 10.18, and 13.89 μ, among others. The n.m.r. spectrum (22%, deuteriochloroform) of the compound is given as Figure 7.

A small portion of the compound was recrystallized twice from 80 per cent ethanol for elemental analysis. The analytical sample showed m.p. 115.5-116°.

Anal. $C_{15}H_{16}N_2O_9$ (368.3) Calc'd: C, 48.92; H, 4.38; N, 7.61
Found : C, 48.73; H, 4.44; N, 7.75

1,2-O-Isopropylidene-3-O-(p-toluenesulfonyl)-5-deoxy-β-L-arabinofuranose. A solution of 3.138 g. (18.0 mmole) of 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose in 80 ml. of anhydrous pyridine was cooled to 0°. p-Toluenesulfonyl chloride (10.198 g., 53.5 mmole) was added in small portions. The resulting yellow solution was allowed to stand at room temperature for two days. The brown reaction mixture was poured, with stirring, into 150 ml. of an ice-water mixture. The mixture was stirred for 30 min. and then extracted with three 150-ml. portions of chloroform. The combined extract was dried and evaporated. The syrupy product (6.156 g., 104%) was chromatographed over silicic acid (50.0 g., column 10.7 cm. x 3.6 cm.) using chloroform (fraction volume, 25 ml.). The product (4.497 g., 76%) was eluted in fractions 5-12 and was a colorless crystalline solid. After recrystallization from ligroine (b.p. 100-110°), the product (3.160 g., 54%) showed m.p. 53.5-54.5° and $[\alpha]_D^{24}$ -17.5 ± 0.6° (c 3.25, chloroform). The infrared spectrum (pellet) of the compound showed λ_{max} 3.33, 6.26, 7.34, 8.51, 9.16, and 10.27 μ, among others. The n.m.r. spectrum (25%, deuteriochloroform) of the compound is given as Figure 8.

A small portion of the compound was recrystallized twice from ligroine (b.p. 100-110°) for elemental analysis. The analytical sample showed m.p. 54.0-54.5°.

Anal. $C_{15}H_{20}SO_6$ (328.4) Calc'd: C, 54.86; H, 6.14; S, 9.77
Found : C, 55.10; H, 6.32; S, 8.60

Attempted Oxidations of 1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose.

Chromium trioxide-pyridine oxidations. Several attempts were made to oxidize 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose using the chromium trioxide-pyridine complex. The pertinent data regarding the procedures and results are given in Table 3. The chromium trioxide-pyridine complex was prepared* (using the indicated molar ratio of chromium trioxide to starting alcohol) as a ten per cent slurry in anhydrous pyridine. 1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose was added as a ten per cent solution in anhydrous pyridine. The resulting mixture was stirred at the indicated temperature for the indicated time interval. The reaction was then processed in any of four ways.

The following procedure constitutes procedure A. The pyridine was evaporated *in vacuo* at temperatures below 45°. The brown semi-solid residue was triturated with several large portions of boiling chloroform. The extracts were filtered through celite on sintered glass, dried, and evaporated. The dark syrupy residue was chromatographed on silicic acid. For a typical reaction 20 g. of silicic acid was used (column 8.3 cm. x 2.3 cm.) for 1.0 g. of 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose. The column was eluted with chloroform (fraction volume, 30 ml.). The infrared spectrum (liquid film) was determined for the identification (and as a measure of purity) of the major constituent of each band. Material that showed absorption at 5-6 μ was usually eluted in fractions 3-6. Starting material was recovered from fractions 8-14. Procedure B

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* See page 17, this thesis.

was identical to procedure A except that the chloroform extract was washed with 2 N hydrochloric acid prior to drying and evaporation. Procedure C was identical to procedure B except that the chloroform extract was washed with water instead of 2 N hydrochloric acid. Procedures D and A were identical except that redistilled isopropyl alcohol was added (25 ml. for the usual 1.0 g. reaction) before the pyridine was removed. The solution was stirred for one hour before evaporation of the solvent.

Table 3. Summary of the Attempts to Oxidize 1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose with the Chromium Trioxide-pyridine Complex.

Reaction	Reagent Ratio[a]	Time (Hours)	Temp.	Isolation Procedure	Yield[b] Reactant	Yield[b] Product
1	10	24	20°	B	0	0
2	10	22	25°	C	30	5
3	3	24	25°	C	23	1
4	10	4	26°	C	34	12
5	3	4	26°	A	53	8
6	30	3	0°	A	50	11
7	10	24	0°	D	98	1
8	10	24	27°	D	28	15
9	10	11	26°	D	56	6

[a] The reagent ratio is the ratio of the number of moles of chromium trioxide to the number of moles of reactant used in the reaction.

[b] The yield is that obtained after chromatography and does not reflect the purity of the products. The reactant column lists the percentage of recovered starting material. The product column lists the yield of desired product (presumed present from the infrared spectra). All yields are % by weight.

Chromium trioxide-acetone oxidations. Anhydrous chromium trioxide (1.152 g., 11.5 mmole) was added in small portions to a cooled (10°) and well stirred mixture of 6.0 g. of anhydrous copper sulfate and 50 ml. of anhydrous acetone. A solution of 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose (1.023 g., 5.87 mmole) in 12 ml. of anhydrous acetone was added. The mixture was stirred overnight at room temperature. Redistilled isopropyl alcohol (5.25 ml., 68.7 mmole) was added and the stirring was continued for three hours. The solids were filtered with suction using a celite mat on sintered glass, and then were triturated with three 35-ml. portions of anhydrous acetone. The extracts were filtered with suction and all the acetone solutions were combined and evaporated. The black syrupy residue was chromatographed using chloroform and silicic acid as previously described.* The yield was 0.060 g. (6%) of the desired product (inferred from the infrared spectrum) and 0.565 g. (55.2%) of starting material.

The second attempted oxidation was identical to the first with the following exceptions. The reaction solution was boiled under reflux with stirring for one day. After the addition of 5.25 ml. of redistilled isopropyl alcohol, the mixture was boiled under reflux for 30 min. From 1.002 g. (5.75 mmole) of 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose, there was obtained (after chromatography) 0.088 g. (8.9%) of the desired product and 0.494 g. (49.3%) of the starting material.

The third attempted oxidation was identical to the second with the following exceptions. A larger amount of anhydrous chromium trioxide

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* See page 46, this thesis.

(2.905 g., 29.1 mmole) was used for 1.027 g. (5.89 mmole) of starting material. The reaction mixture was boiled under reflux for 30 min. after the addition of 13.2 ml. (173 mmole) of redistilled isopropyl alcohol. After chromatography there was obtained 0.114 g. (11.2%) of the desired product and 0.281 g. (27.4%) of starting material.

Oppenauer oxidations. A solution of 1.022 g. (5.87 mmole) of 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose, 30.0 ml. (0.408 mole) of anhydrous acetone and 35 ml. of anhydrous benzene was heated under reflux. A filtered solution of 2.029 g. (8.25 mmole) of anhydrous aluminum tert-butoxide in 15 ml. of anhydrous benzene was added and the solution was boiled under reflux for eight hours. The solvent was evaporated and the cream-colored residue was triturated with five 50-ml. portions of boiling chloroform. The extracts were combined, dried, and evaporated. The residue was a white crystalline solid that weighed 0.895 g. The infrared spectrum (chloroform solution) of the product was superimposable with that of the starting material.

Another oxidation attempt was made using p-benzoquinone and aluminum tert-butoxide. A solution of 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose (1.012 g., 5.75 mmole), recrystallized p-benzoquinone (12.057 g., 111 mmole), anhydrous benzene (120 ml.), and anhydrous aluminum tert-butoxide (2.032 g., 8.26 mmole) was boiled under reflux for 6.5 hr. The solvent was evaporated and the residue was triturated with five 150-ml. portions of chloroform. The extracts were combined and concentrated to about 100 ml. This solution was extracted with four 100-ml. portions of distilled water. After combination, the aqueous extracts were continuously extracted with chloroform for one day. The chloroform

extract was dried and evaporated. The residue (1.706 g.) was chromatographed using chloroform and silicic acid (50 g., column 10.2 cm. x 3.3 cm.; fraction volume, 20 ml.). Fractions 1-4 contained p-benzoquinone (1.368 g.). The infrared spectrum of this material was superimposable with that of the reagent. Fractions 5-9 contained only traces of material. Fractions 10-13 contained 0.075 g. of starting material. No material was obtained from further elution (600 ml.) of the column.

Catalytic oxidation. A mixture of 10.16 g. of ten per cent platinum on carbon (Baker) and 35 ml. of distilled water was equilibrated with oxygen (1 atm.) in a closed system. The mixture was stirred at 27° during the equilibration, and the consumption of oxygen was followed volumetrically. The sample, 0.529 g. (3.04 mmole) of 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose dissolved in 5 ml. of distilled water, was added to the mixture. Care was taken to prevent air from entering the system during the addition. The vigorously stirred mixture consumed 2.50 mmole (82% of the required amount) of oxygen slowly over two days. After the consumption of oxygen ceased, the catalyst was filtered and washed well with ethanol. The solvent was evaporated and the product (0.317 g., 60%) was air-dried. The infrared spectrum (chloroform solution) of the crystalline product showed negligible absorption in the region 5-6 μ and was essentially superimposable with that of the starting material.

Attempted Oxidation of 1,2-O-Isopropylidene-3-O-(p-toluenesulfonyl)-5-deoxy-β-L-arabinofuranose.

The oxidation of l-menthyl tosylate. l-Menthyl tosylate was prepared as described elsewhere (57). From 7.982 g. (0.0512 mole) of

l-menthol and 19.60 g. (0.103 mole) of p-toluenesulfonyl chloride, there was obtained 12.359 g. (84%) of white crystals, m.p. 92-93° [lit. (57) m.p. 94-95°].

A mixture of 75 ml. of dimethyl sulfoxide and 11.0 g. of sodium bicarbonate was heated to 100° during ebullition using dry nitrogen. After the addition of l-menthyl tosylate (5.032 g., 16.4 mmole), the mixture was maintained at 100° during ebullition using dry nitrogen for 30 min. The mixture was cooled and poured into 135 ml. of 2,4-dinitrophenylhydrazine reagent (58), which contained 4.0 g. (20.2 mmole) of 2,4-dinitrophenylhydrazine. A yellow precipitate formed immediately. The mixture was warmed on the steam bath for 20 min. After cooling, the solids were filtered with suction and washed thoroughly with 1:1 ethanol-water. The solids were air-dried and triturated with four 30-ml. portions of chloroform. The extracts yielded 2.080 g. of orange crystals after evaporation. After recrystallization from 95 per cent ethanol (25 ml.), the product (0.786 g.) was composed of two kinds of crystals. A few of the orange crystals were manually removed from the mixture and showed m.p. 143-144.5° [lit. (59), l-menthone 2,4-dinitrophenylhydrazone m.p. 144°]. Similarly, a few of the colorless crystals were separated and melted at 90-91.5° [l-menthyl tosylate, m.p. 92-93°].

The attempted oxidation of 1,2-O-isopropylidene-3-O-(p-toluenesulfonyl)-5-deoxy-β-L-arabinofuranose. A well stirred mixture of dimethyl sulfoxide (35 ml.) and sodium bicarbonate (4.00 g.) was heated to 150°. Ebullition with dry nitrogen was maintained throughout the reaction. A solution of 1,2-O-isopropylidene-3-O-(p-toluenesulfonyl)-5-deoxy-β-L-arabinofuranose (0.727 g., 2.22 mmole) in dimethyl sulfoxide (2 ml.) was

added in one portion. The mixture was stirred at 150° for three hours. After cooling, the solids were filtered with suction and washed with dimethyl sulfoxide (5 ml.). The filtrate was lyopholized. The residue was triturated with 50 ml. of chloroform. After evaporation, the extract yielded 0.721 g. (99.3%) of colorless crystalline material, m.p. 52-54°. The infrared spectrum (chloroform solution) of the product was identical to that of the starting material.

Oxidation of Borneol. A solution containing anhydrous pyridinium phosphate* (2.90 g., 16.3 mmole), N,N'-dicyclohexylcarbodiimide (20.251 g., 97.5 mmole, Eastman, m.p. 31-35°) and 80 ml. of dimethyl sulfoxide-benzene (1:1)** was allowed to stand at room temperature for 15 min. before the addition of borneol (4.990 g., 32.5 mmole, Eastman). The reaction was allowed to stand at room temperature for 22 hr. during which time a small amount of N,N'-dicyclohexylurea precipitated. The benzene was evaporated, ethanol (40 ml., 95%) was added, and the solids were filtered with suction. The filtrate was poured, with stirring, into 400 ml. of 2,4-dinitrophenylhydrazine reagent (58) which contained 12.0 g., 60.6 mmole, of 2,4-dinitrophenylhydrazine. The solution was warmed on the steam bath for 35 min. and cooled in the refrigerator overnight. The yield of filtered, air-dried crystals was 5.664 g. (52%), m.p. 173-174.5° [lit. (60), d-camphor 2,4-dinitrophenylhydrazone, m.p. 174°].

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* Prepared by adding 0.11 mole of anhydrous pyridine to 0.10 mole of 85 per cent phosphoric acid (with cooling). The resulting semi-solid was dried in vacuo at room temperature for four days immediately prior to use.

** Prepared by drying a solution of anhydrous benzene and dimethyl sulfoxide under a Dean-Stark trap for four days immediately prior to use.

1,2-O-Isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose.

N,N'-Dicyclohexylcarbodiimide (35.459 g., 0.195 mole) and pyridinium phosphate* (5.165 g., 0.029 mole) were dissolved in 160 ml. of dimethyl sulfoxide-benzene (1:1).* The resulting solution was allowed to stand at room temperature for 30 min. During this period a small amount of N,N'-dicyclohexylurea precipitated. 1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose (10.023 g., 57.4 mmole) was added and the mixture was shaken vigorously. The mixture was then allowed to stand at room temperature for 11 hr. After 38.8 ml. (0.516 mole) of isopropyl alcohol was added, the mixture was allowed to stand for an additional four hours. The N,N'-dicyclohexylurea was filtered with suction and washed with 50 ml. of dry dimethyl sulfoxide-benzene (1:1). The filtrate was lyopholized at pressures below 150 μ. The lyopholization was continued until the residue was a yellow semi-solid. The sublimate was allowed to melt and the resulting colorless solution was set aside. The residue was triturated with two 200-ml. portions of boiling, redistilled cyclohexane. The extracts were combined and evaporated. This residue was dissolved in 50 ml. of dimethyl sulfoxide. The solution was lyopholized as described above. This sublimate was combined with that previously set aside. The resulting solution was diluted with an equal volume of distilled water. The solution was continuously extracted with redistilled cyclohexane for five days. The cyclohexane extract was dried and evaporated. The product (5.543 g., 56%) was a colorless, mobile liquid. A small amount of solid N,N'-dicyclohexylurea was present as an impurity.

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* See page 52, this thesis.

The aqueous dimethyl sulfoxide was continuously extracted for an additional five days. The extract after drying and evaporation yielded an additional 0.317 g. (3%) of colorless liquid.

A small amount of the product was present in the cyclohexane which had been evaporated from the extracts. Three successive distillations of this cyclohexane yielded a total residue of 0.447 g. (4%) of colorless liquid. The product that was obtained in this manner had no discernable impurities. All of the physical properties and spectra presented were recorded using material of this purity. The specific rotation of the product was $[\alpha]_D^{28}$ +75.7 ± 1.3° (c 2.30, chloroform). The infrared spectrum (liquid film) is shown as Figure 9. The n.m.r. spectrum (40%, deuteriochloroform) of the compound is given as Figure 10.

The total yield of 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose was 6.307 g. (63.8%). The yield varied from 51 to 72 per cent in other, similar preparations.

TLC (silica gel G, detection by iodine) analysis of the compound showed only one spot using both chloroform (R_F 0.31) and 3:1 chloroform-hexane (R_F 0.25).

The compound partially decomposed if allowed to stand neat or in chloroform solution at room temperature for several days as evidenced by severe discoloration and marked changes in the infrared and n.m.r. spectra. Attempted purification of the compound by silicic acid chromatography (using chloroform as the eluting agent) resulted in similar decomposition. The compound was stable for at least two weeks when frozen in cyclohexane at -80°.

1,2-O-Isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose Oxime. A solution containing hydroxylamine hydrochloride (0.4557 g., 6.61 mmole), distilled water (3 ml.), aqueous 10 per cent sodium hydroxide (25 ml.), ethanol (5 ml.), and 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose (0.1437 g., 0.84 mmole) was boiled for 15 min., cooled, and extracted with three 30-ml. portions of chloroform. The extracts were combined, dried, and evaporated. During refrigeration for three days, the colorless residue (0.1751 g., 110%) crystallized. Two recrystallizations from petroleum ether (b.p. 60-90°) yielded 0.0420 g. (27%), m.p. 103-105°, $[\alpha]_D^{23}$ -10.1 ± 0.4° (c 4.87, chloroform). The product was sublimed (60-70°, 0.5 mm.). The sublimate weighed 0.0367 g. and melted at 104-105.5° (sealed tube).

Anal.	$C_8H_{13}NO_4$	Calc'd:	C, 51.33; H, 7.00; N, 7.48
	(187.2)	Found :	C, 51.52; H, 6.91; N, 7.61

The infrared spectrum (pellet) of the compound showed λ_{max} 2.95, 3.33, 6.22, 7.30, 8.23, 9.06, 9.52, 10.53, and 11.56 μ, among others. The n.m.r. spectrum (15%, deuteriochloroform) of the compound showed absorption at 8.62 (3H, singlet), 8.43 (3H, doublet, J = 6.77), 8.41 (3H, singlet), 5.02 (1H, quartet, J = 6.71), 5.11 (1H, doublet, J = 3.90), 4.13 (1H, doublet, J = 4.06), and 1.00 τ (1H, broad singlet).

Synthesis of 2,3-O-Isopropylidene-5-deoxy-L-arabinose Diethyl Dithioacetal

5-Deoxy-L-arabinose Diethyl Dithioacetal. A solution of crude 5-deoxy-L-arabinose (7.486 g., 55.8 mmole) in 12 N hydrochloric acid (15 ml.) was cooled in an ice bath for 15 min. Ethanethiol (11.0 ml., 9.2 g., 211 mmole) was added and the mixture was swirled vigorously for 20 min. The product began to precipitate when a few small pieces of ice were

added. Cold water (35 ml.) was added and the mixture was stirred for 10 min. The solids were filtered with suction and recrystallized from distilled water. The white crystals (3.129 g., 23.3%) melted at 110-111.5° $[\alpha]_D^{27}$ +9.8 ± 1.1° (c 1.92, dry pyridine) [lit. (55), m.p. 108-109°, $[\alpha]_D^{26}$ +11.9° (c 1.936, dry pyridine)]. Concentration of the mother liquors yielded an additional 1.163 g. (8.6%).

The n.m.r. spectrum (saturated deuteriochloroform solution) showed absorption at 8.72 (6H, triplet, J = 7), 8.71 (3H, doublet, J = 6), 7.30 and 7.26 (4H, two quartets, J = 7), 6.87 (3H, broad, singlet), and 5.87-6.27 τ (4H, overlapping multiplets).

2,3-O-Isopropylidene-5-deoxy-L-arabinose Diethyl Dithioacetal. A mixture of 5-deoxy-L-arabinose diethyl dithioacetal (0.254 g., 1.06 mmole), anhydrous copper sulfate (2.0 g.), anhydrous acetone (20.0 ml., 0.43 mole), and one drop of 98 per cent sulfuric acid was stirred at room temperature for 22 hr. After the addition of anhydrous calcium oxide (1.5 g.), the mixture was stirred for 1.5 hr. The solids were filtered with suction and washed with anhydrous acetone. The filtrate was evaporated and yielded 0.310 g. of a viscous yellow liquid. The product was chromatographed on silicic acid (4.50 g., column 9.0 cm. x 1.1 cm.) using chloroform (fraction volume, 5 ml.). Fractions 1-2 contained no material. Fractions 3-6 were combined and contained 0.195 g. (66%) of syrupy 2,3-O-isopropylidene-5-deoxy-L-arabinose diethyl dithioacetal. Fractions 7-9 contained no material. Fractions 10-22 contained 0.034 g. of crystalline starting material (m.p. 109-111°). The product resisted crystallization and showed $[\alpha]_D^{25}$ -66.3 ± 0.9° (c 2.48, chloroform). GLC (SE-30, A.I.P. 15 psig, C.T. 165°) analysis of the compound showed only one peak (R.T. 6.05 min.). The

infrared spectrum (liquid film) of the compound showed λ_{max} 2.83, 3.33, 6.90, 7.29, 8.17, 9.18, and 11.32 μ, among others. The n.m.r. spectrum (13%, deuteriochloroform) of the compound is given as Figure 11.

The compound was observed to give a positive iodoform test (61). The precipitate was collected and showed m.p. 121.5-122.5°. The melting point of the precipitate mixed with authentic iodoform (m.p. 122°) was 121.5-122°.

2,3-O-Isopropylidene-4-O-(3,5-dinitrobenzoyl)-5-deoxy-L-arabinose Diethyl Dithioacetal. A solution of 2,3-O-isopropylidene-5-deoxy-L-arabinose diethyl dithioacetal (0.577 g., 2.05 mmole) and recrystallized 3,5-dinitrobenzoyl chloride (1.478 g., 6.4 mmole) in anhydrous pyridine (20 ml.) was maintained at 80° for one hour. The cooled solution was poured into saturated aqueous sodium bicarbonate (50 ml.) and stirred for 30 min. The mixture was extracted with four 75-ml. portions of chloroform. The combined extract was washed with two 200-ml. portions of 2 N hydrochloric acid and 100 ml. of saturated aqueous sodium bicarbonate. The solution was dried and evaporated and yielded 1.043 g. (108%) of yellow syrup. The residue was chromatographed using silicic acid (20 g., column 9.5 cm. x 2.3 cm.) and chloroform (fraction volume, 20 ml.). Fraction 1 contained no material. Fractions 2-4 contained 0.754 g. (78%) of the desired product. After crystallization from redistilled hexane there was obtained 0.203 g. (21%) of yellow crystals, m.p. 55-58°, $[\alpha]_D^{27}$ -12.0 ± 0.6° (c 3.08, chloroform). The infrared spectrum (pellet) showed λ_{max} 3.32, 5.76, 6.14, 6.47, 7.45, 8.57, 9.51, and 13.85 μ, among others. The n.m.r. spectrum (30%, carbon tetrachloride) of the compound showed absorption at 8.78 (6H, triplet, J = 7), 8.61 (6H, singlet), 8.52 (3H,

doublet, J = 6.5), 7.33 and 7.37 (4H, two quartets, J = 7), 6.19 (1H, doublet, J = 5.5), 5.93 (1H, triplet, J = 5.8), 5.73 (1H, triplet, J = 5.8), 4.78 (1H, quintet, J = 6.0), and 0.94 τ (3H, broad singlet).

A small portion of the compound was recrystallized from redistilled hexane for elemental analysis. The analytical sample showed m.p. 59.0-60.5°.

Anal. $C_{19}H_{26}N_2S_2O_8$ (474.6) Calc'd: C, 48.09; H, 5.52; N, 5.90; S, 13.51
Found : C, 48.13; H, 5.61; N, 5.88; S, 13.65

Attempts to Obtain a Methylene Derivative of 5-Deoxy-L-arabinose Diethyl Dithioacetal.

Methylenation in Water. 5-Deoxy-L-arabinose diethyl dithioacetal (0.130 g., 0.54 mmole), paraformaldehyde (0.190 g., 4.1 mmole), and 12 N hydrochloric acid (0.2 ml.) were mixed and heated on a steam bath for 10 min. Water (25 ml.) was added and the mixture was extracted with four 25-ml. portions of chloroform. The extracts were combined, dried, and evaporated. The residue, 0.061 g., was a yellow syrup. The n.m.r. spectrum (20%, deuteriochloroform) of the product showed absorption at 8.72 (6H*, triplet, J = 7), 8.71 (3H*, doublet, J = 6), 7.82 (3.72H, singlet), 7.30 and 7.26 (6.50 H, two quartets, J = 7), 7.10 (3.00 H, broad singlet), 6.70 (1.31H, singlet), and 4.6-6.3 τ (13.53H, unresolved multiplets).

Methylenation in aqueous dioxane. A solution containing 5-deoxy-L-arabinose diethyl dithioacetal (0.910 g., 3.78 mmole) and 40 per cent aqueous formaldehyde (5.0 ml., 42.5 mmole, Eastman) was cooled to 0°

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* Assumed.

and saturated with anhydrous hydrogen chloride. The solution was stirred for one hour at 0° and allowed to stand in the refrigerator overnight. The solution was poured into 50 ml. of an ice-water mixture. The resulting mixture was extracted with three 80-ml. portions of chloroform. The extracts were combined, dried, and evaporated. The residue was 0.344 g. of a yellow liquid. The n.m.r. spectrum (23%, deuteriochloroform) showed absorption at 8.7 (doublet, J = 6), and 4.0-6.8 τ (unresolved multiplets). No absorption was observed from 6.8 τ to 8.5 τ.

Methylenation in anhydrous dioxane. A mixture of 5-deoxy-L-arabinose diethyl dithioacetal (0.502 g., 2.08 mmole), dioxane (25 ml., dried with anhydrous copper sulfate), paraformaldehyde (1.028 g., 22.4 mmole), anhydrous copper sulfate (5.0 g.), and 15 drops of 98 per cent sulfuric acid was stirred at room temperature overnight. After 5.0 g. of anhydrous calcium oxide was added, the mixture was stirred for 30 min. The solids were removed by suction filtration using a celite mat on sintered glass. The filtrate was evaporated and yielded 0.514 g. of a yellow syrup. The n.m.r. spectrum (15%, deuteriochloroform) showed absorptions at 8.68 (doublet, J = 6), 4.7-6.4 (unresolved multiplets), 4.91 (doublet, J = 4), and 4.19 τ (doublet, J = 4). No appreciable absorption was observed between 6.4 and 8.5 τ.

Attempted Synthesis of Dideoxydihydrostreptose

1,2-O-Isopropylidene-3-C-methyl-5-deoxy-β-L-lyxofuranose. The reaction, in anhydrous ether, between 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose and methylmagnesium iodide was performed in the same manner as a different reaction that was described previously.*

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* See page 25, this thesis.

When 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose (2.699 g., 15.6 mmole), magnesium (3.942 g., 0.164 mole), and methyl iodide (33.1 g., 0.233 mole) were used, there was obtained (from the ether extract) 2.625 g. (89%) of crystalline material.

The crude product was sublimed *in vacuo* (26-44°, 0.15 mm.) and yielded 1.451 g. of white crystals. GLC (EGA, A.I.P. 15 psig, C.T. 70°) analysis of the sublimate showed two peaks at R.T. 6.18 min. (area *ca.* 1 in.^{2}) and 12.84 min. (area *ca.* 7 in.^{2}). The infrared spectrum (chloroform solution) showed λ_{max} 5.64 μ, among others. The sublimate and residue were combined (2.243 g.) and chromatographed over silicic acid (30.0 g., column 14.5 cm. x 2.2 cm.) using chloroform (fraction volume, 50 ml.). Fractions 1-4 contained no material. Fractions 5-9 contained 0.886 g. (30%) of colorless crystals. Fractions 10-35 contained 0.189 g. of yellow syrup. Fractions 36-50 (eluted with 1% methanol in chloroform) contained 0.229 g. of orange syrup. GLC (EGA, A.I.P. 15 psig, C.T. 70°) analysis of fractions 5-9 (combined) showed only one component (R.T. 12.19 min.).

The infrared spectrum (pellet) of the compound showed λ_{max} 2.80, 3.31, 6.92, 7.34, 8.27, 9.27, and 11.42 μ, among others. The n.m.r. spectrum (15%, deuteriochloroform) of the compound is given as Figure 12.

A small portion of the compound was sublimed twice for elemental analysis. The analytical sample showed m.p. 115.5-117.5° (sealed tube) and $[\alpha]_D^{27}$ -6.8 ± 0.9° (*c* 2.05, chloroform).

Anal. $C_9H_{16}O_4$ (188.2) Calc'd: C, 57.43; H, 8.57
Found : C, 57.51; H, 8.48

Attempts to Obtain and Desulfurize an Ethyl Thioglycoside of 3-*C*-Methyl-5-deoxy-L-lyxose. Anhydrous sodium sulfate (3.0 g.) was added to a solution of 1,2-*O*-isopropylidene-3-*C*-methyl-5-deoxy-β-L-lyxofuranose (0.578 g., 3.07 mmole), anhydrous zinc chloride (1.0 g.), and anhydrous ethanethiol (20.0 ml.). The mixture was stirred vigorously at 0° for one day. Saturated aqueous sodium bicarbonate (70 ml.) was added and the mixture was stirred for 30 min. The solids were filtered with suction and triturated with three 50-ml. portions of boiling chloroform. The aqueous filtrate was extracted with six 100-ml. portions of chloroform. All of the extracts were combined, dried, and evaporated. The residue (0.612 g.) was a viscous orange syrup. The n.m.r. spectrum (40%, deuteriochloroform) of the residue showed absorption at 8.61-8.91 (overlapping multiplets, area = 16.7), 8.42 (singlet, area = 1.7), 7.26 and 7.42 (two quartets, *J* = 7, total area = 6.0), and 5.82-6.40 τ (overlapping multiplets, area = 7.3).

The residue was dissolved in 40 ml. of 7:3 ethanol-water and 10 ml. (allowed to settle in a graduated cylinder) of Raney nickel (Raney Catalyst Co.) was added. The mixture was boiled under reflux for four hours. The solids were removed by suction filtration, using a celite mat on sintered glass and were washed thoroughly with boiling ethanol. The filtrate was concentrated to *ca*. 25 ml. and extracted with five 50-ml. portions of chloroform. The combined extract was dried and evaporated and gave 79 mg. (19%, yield) of orange syrup. The n.m.r. spectrum (10%, deuteriochloroform) of the syrup showed absorption at 8.6-9.0 (broad) and 5.1-6.5 τ (broad). Both the lack of resolution of peaks and the width of the absorption indicated that this preparation was a complicated mixture.

A mixture of anhydrous sodium sulfate (3.0 g.), 1,2-O-isopropylidene-3-C-methyl-5-deoxy-β-L-lyxofuranose (0.452 g., 2.40 mmole), anhydrous zinc chloride (1.0 g.), and anhydrous ethanethiol (30 ml.) was stirred at room temperature for six days. The product was isolated as described above. The n.m.r. spectrum (20%, deuteriochloroform) of the residue (0.368 g.) showed absorptions at 8.60-8.83 (overlapping multiplets, area = 20.4), 7.10-7.47 (overlapping quartets, area = 4.7), 5.83-6.48 (overlapping multiplets, area = 8.4), and 4.95 τ (doublet, J = 7, area = 0.7).

The residue was dissolved in 20 ml. of 7:3 ethanol-water, 5 ml. of wet Raney nickel was added and the mixture was boiled under reflux for four hours. The product was isolated as described above. The residue (0.135 g., 42% overall yield) was sublimed *in vacuo* (26-60°, 0.08 mm.) and yielded 60 mg. of colorless syrup. GLC (SE-30, A.I.P. 10 psig, C.T. 66°) analysis of the product showed peaks at R.T. 3.57 (area, 0.22 $in.^2$), 3.86 (area, 0.25 $in.^2$), 4.06 (area, 0.22 $in.^2$), 4.38 (area, 0.48 $in.^2$), 6.75 (area, 0.11 $in.^2$), and 7.53 min. (area, 0.49 $in.^2$). Under the same conditions GLC analysis of a sample of authentic dideoxydihydrostreptose* prepared as described elsewhere (62) from streptomycin, showed only one peak (R.T. 3.41 min.).

A mixture of anhydrous sodium sulfate (3.0 g.), 1,2-O-isopropylidene-3-C-methyl-5-deoxy-β-L-lyxofuranose (0.587 g., 3.11 mmole), anhydrous zinc chloride (1.0 g.), and anhydrous ethanethiol (30 ml.) was maintained at 35° in a closed container for 54.0 hr. After cooling, the

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* The author is very grateful to Mr. R. K. Chawla for this sample.

product was isolated as described above. The residue (0.935 g.) was dissolved in chloroform (30 ml.) and extracted with three 40-ml. portions of water. The combined aqueous extract was extracted with ten 100-ml. portions of chloroform. The combined chloroform extract was dried, evaporated, and yielded 0.213 g. of colorless syrup. The n.m.r. spectrum (20%, deuteriochloroform) of the syrup showed absorptions at 8.77 and 8.72 (doublet, J = 7; triplet, J = 8; total area = 20.2), 7.31 (quartet, J = 8, area = 4.8), 6.57 (broad singlet, area = 4.6), 6.02 and 6.24 (quartet, J = 7; doublet, J = 6; total area = 4.8), and 4.95 τ (doublet, J = 6, area = 1.3). The spectrum contained several other smaller peaks.

The residue was dissolved in 25 ml. of 7:3 ethanol-water and 3 ml. of wet Raney nickel was added. The mixture was boiled under reflux for four hours. The product was isolated as described above. The n.m.r. spectrum (10%, deuteriochloroform) of the crude product (0.111 g., 26% overall yield) showed broad, partially resolved absorption at 8.66-8.92 and 6.05-6.82 τ. GLC (SE-30, A.I.P. 10 psig, C.T. 66°) analysis of the product showed peaks at R.T. 3.43 (area, 0.05 $in.^2$), 3.88 (area, 0.12 $in.^2$), 4.29 (area, 0.25 $in.^2$), 6.82 (area, 0.09 $in.^2$), and 7.33 min. (area 1.77 $in.^2$).

Several other similar (different conditions) mercaptolysis and desulfurization reactions gave results similar to those described above.

Synthesis of L-Dihydrostreptose

1,2-O-Isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose. The Grignard reaction was performed in the same manner as a different reaction that was described previously.* When 6.171 g. (35.8 mmole) of 1,2-O-

* See page 25, this thesis.

isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose, 8.10 g. (0.333 mole) of magnesium and 42.8 g. (0.40 mole) of vinyl bromide were used, there was obtained 7.460 g. (104%) of yellow crystals. GLC (SE-30, A.I.P. 10 psig, C.T. 100°) analysis of the product showed only one peak (R.T. 5.88 min.) up to R.T. 35 min. The product was purified by fractional vacuum sublimation using a cold water (0°) condenser. Fraction one (27°, 0.5-0.2 mm.) contained 0.764 g. (11%) of white crystals, m.p. 53-62°. Fraction two (26°, 0.15 mm.) contained 4.184 g. (58%) of white crystals, m.p. 66-67.5°. Fraction three (26°, 0.09 mm.) contained 0.103 g. (1.4%) of white crystals, m.p. 62-65.5°.

The infrared spectrum (pellet) of the compound showed λ_{max} 2.78, 3.29, 6.08, 7.21, 8.23, 9.28, 10.83, and 11.38 μ, among others. The n.m.r. spectrum (27%, deuteriochloroform) of the compound is given as Figure 13.

A small portion of the compound was sublimed twice for elemental analysis. The analytical sample showed m.p. 67.5-68.5° and $[\alpha]_D^{27}$ +21.1 ± 0.6° (c 3.08, chloroform).

Anal.	$C_{10}H_{16}O_4$	Calc'd:	C, 59.98; H, 8.06
	(200.2)	Found :	C, 60.19; H, 8.29

GLC (same conditions) analysis of the analytical sample showed only one peak (R.T. 5.95 min.).

The sublimation residues and washings from several identical preparations were combined (4.064 g.) and chromatographed using silicic acid (100 g., column 17.0 cm. x 3.4 cm.) and chloroform (fraction volume, 50 ml.). Fractions 1-8 contained 0.335 g. of yellow syrup. Fractions 9-14 contained 0.769 g. of white crystalline 1,2-O-isopropylidene-3-C-vinyl-

5-deoxy-β-L-lyxofuranose. Fractions 15-45 (eluted with 1% methanol in chloroform) contained 1.314 g. of a mixture of white solid and yellow syrup. Fractions 46-67 (eluted with 2% methanol in chloroform) contained 0.754 g. of an orange syrup.

Fractions 15-45 were combined and dissolved in boiling, anhydrous methanol. Water was added dropwise until the solution became cloudy. On cooling, 71 mg. of white crystals were obtained. This material was recrystallized from methanol-water and showed m.p. 221-222.5° and $[\alpha]_D$ +0.3 ± 0.3° (c 1.56, methanol). The compound was appreciably soluble only in methanol. These properties, as well as the infrared spectrum (pellet) of the compound, are identical to those of N,N'-dicyclohexylurea. The melting point of a mixture of a recrystallized portion of the compound (m.p. 222.5-223°) and an authentic sample of N,N'-dicyclohexylurea was not depressed.

The remainder of the material from fractions 15-45 and that from fractions 46-67 were viscous syrups that exhibited ill-defined n.m.r. spectra. TLC analysis (silica gel G, chloroform, detection by iodine) of these syrups showed at least six overlapping spots at R_F 0.0-0.6.

1,2-O-Isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose. A mixture of ozone in oxygen was bubbled through a solution of 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (0.556 g., 2.77 mmole) in anhydrous ethyl acetate (50 ml.) for 16 min. (total ozone, 8.0 mmole) at -81°. The blue solution was added immediately in a steady stream to a well stirred, cooled (0°) solution of sodium borohydride (0.414 g., 11 mmole), anhydrous ethyl acetate (30 ml.), and anhydrous ethanol (20 ml.). The solution was stirred at 0° for 30 min. and then boiled under reflux

for one hour. The cooled solution was diluted with distilled water (100 ml.) and extracted with four 200-ml. portions of chloroform. The combined extracts were dried and evaporated. The residue was a white solid that slowly crystallized (m.p. 100.5-104.5°). The residue was sublimed (50-55°) in vacuo (0.10 mm.) and yielded 0.399 g. (71%) of white crystals, m.p. 103.5-105.5°, $[\alpha]_D^{26}$ +7.6 ± 0.5° (c 4.21, methanol). The infrared spectrum of the compound showed λ_{max} 2.80, 3.30, 7.22, 8.67, 9.16, 10.06, and 11.38 μ, among others. The n.m.r. spectrum (10%, deuteriochloroform) of the compound is given as Figure 14.

A small portion of the compound was resublimed twice for elemental analysis. The analytical sample showed m.p. 104-106°.

Anal. $C_9H_{16}O_5$ (204.2) Calc'd: C, 52.93; H, 7.90
Found : C, 52.91; H, 7.82

Stability of 1,2-O-Isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose to Acid. A mixture of 1,2-O-isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose (19.7 mg.), water (1 ml.), and Dowex 50W-X8 (H^+) (0.5 ml.) was stirred at room temperature. A small portion was withdrawn every few hours and chromatographed on paper (BEW, SP and PC). Chromatography of the starting material showed only one faint spot (R_F 0.81). The starting material gave a negative Benedict's test. After 3 hr., two spots were present (R_F 0.8 and 0.5); after 20 hr., the spot at R_F 0.8 no longer appeared. After 44 hr., the intensity of the spot at R_F 0.5 no longer increased. The resin was filtered, and the filtrate gave a strong, positive Benedict's test.

L-Dihydrostreptose. A mixture of 1,2-O-isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose (0.808 g., 3.97 mmole), distilled water

(24 ml.), and Dowex 50W-X8 (H^+) (24 ml.) was stirred at room temperature for 49.0 hr. The resin was filtered and washed thoroughly with distilled water. The filtrate (Benedict's positive) was concentrated to ca. 20 ml. and lyopholized. The yellow syrupy residue was triturated with anhydrous acetone and the solid (resin throw) was removed by centrifugation. The supernatant liquid was evaporated and yielded 0.664 g. (99%) of yellow syrup, $[\alpha]_D^{27}$ (40 min.) -17.6 ± 2.0° (c 1.08, water), $[\alpha]_D^{26}$ (20 hr.) -14.8 ± 2.0°.

The syrup was chromatographed over carbon-celite (60 g., column 66.5 cm. x 1.7 cm., flow rate 21 ml./hr.) and was eluted with distilled water (fraction volume, 50 ml.). The individual fractions were tested with Benedict's reagent before concentration to ca. 10 ml. and lyopholization. Fractions 1-4 were non-reducing and contained 41 mg. of white solid (column throw). Fractions 5-16 were reducing and contained 410 mg. (63%) of colorless syrupy L-dihydrostreptose. Further elution yielded only traces of reducing material. The specific rotation of fractions 11 and 12 (combined) was $[\alpha]_D^{25}$ (20 min.) -21.2 ± 0.5° and $[\alpha]_D^{27}$ (25 hr.) -24.1 ± 0.5° (c 4.12, water).

The infrared spectrum (liquid film) of the compound is given as Figure 15. The n.m.r. spectrum (19%, deuterium oxide, external DSS) is given as Figure 16.

Paper chromatography of the compound showed only one spot (PC) in both EAW (R_F 0.49, R_G 2.88) and BEW (R_F 0.52, R_G 1.68).

L-Dihydrostreptose p-Toluenesulfonylhydrazone. A solution of L-dihydrostreptose (67.3 mg., 0.41 mmole), p-toluenesulfonylhydrazine (63) (74.3 mg., 0.47 mmole), and anhydrous methanol (2 ml.) was boiled

under reflux for 40 min. No solid was observed after the solution was cooled in the refrigerator for two days. The solution was evaporated and anhydrous methanol (1 ml.) and distilled water (10 ml.) were added. There was obtained 4.5 mg. (3.6%) of white crystals after the solution was cooled three days in the refrigerator. The infrared spectrum (pellet) of the compound showed λ_{max} 2.83, 3.05, 6.27, 7.52, 8.64, 9.12, 10.81, and 12.31 μ, among others [lit. (30), λ_{max} (nujol), 2.82, 3.08, 8.70 μ]. A small portion of the product was recrystallized from anhydrous ether-petroleum ether (b.p. 30-60°) and showed m.p. 133-137° [lit. (30), 137.5-138° (dec.)].

Several other attempts (using other conditions) to prepare this derivative failed.

L-Dihydrostreptosonic Acid Lactone. A mixture of L-dihydrostreptose (170 mg., 1.03 mmole, not chromatographed), anhydrous strontium carbonate (1.00 g.), distilled water (35 ml.), and bromine (320 mg., 1.94 mmole) was allowed to stand at room temperature in the dark for four hours. The excess bromine was removed by aeration using dry nitrogen. The solids were filtered and washed well with distilled water. Freshly prepared silver carbonate (1.50 g.) was added and the mixture was shaken for 30 min. The solids were filtered and washed well with water. The filtrate was saturated with hydrogen sulfide and then filtered through a celite mat on sintered glass. The filtrate was concentrated to ca. 20 ml. and lyopholized. The residue (152 mg.) was triturated with two 25-ml. portions of anhydrous acetone. The solids were removed each time by centrifugation (total 55 mg.). The combined supernatant was evaporated and yielded 100.2 mg. (59.7%) of colorless syrup

(the n.m.r. spectrum of this material and that of the final crystalline product were identical). During standing overnight in the refrigerator, the residue crystallized, m.p. 115-130°. A solution of the residue in redistilled 2-butanone (1 ml.) was centrifuged and the supernatant liquid was diluted with chloroform (4 ml.). After cooling overnight, 43.5 mg. (27%) of white crystals (m.p. 137-142°) was obtained and set aside. The filtrate was evaporated. The residue was dried by solution in anhydrous acetone (2 ml.) and anhydrous benzene (50 ml.) followed by evaporation of the solvent. The residue was dissolved in 2-butanone (0.5 ml.); chloroform (2 ml.) was added to the solution and the mixture was centrifuged. The supernatant liquid was diluted with chloroform (10 ml.) and cooled overnight. An additional 14.6 mg. (8.7%) of crystals (m.p. 138.5-142.5°) was obtained. The n.m.r. spectrum (17%, acetone-D_6) of the compound showed absorptions at 8.67 (3H, doublet, J = 6.5), 6.38 (2H, singlet), 5.83 (3H, broad singlet), 5.38 (1H, singlet), and 5.37 τ (1H, quartet, J = 6.5). In addition, the n.m.r. spectrum determined using a sample dissolved in dimethyl sulfoxide-D_6 (5%) showed absorptions at 5.17 (1H, singlet), 4.95 (1H, triplet, J = 4.7), and 4.22 τ (1H, doublet, J = 7.6).

A portion of the compound was recrystallized three times from redistilled 2-butanone and chloroform. The product, after thorough drying *in vacuo* at 50°, showed m.p. 140.5-142.5°, $[\alpha]_D^{25}$ -32.7 ± 0.8 (*c* 1.16 water) [lit. (23), m.p. 143-144°, $[\alpha]_D$ -32° (*c* 0.40, water)]. The infrared spectrum (pellet) showed λ_{max} 2.82, 2.96, 3.41, 5.65, 7.09, 8.62, 9.60, and 11.44 μ, among others [lit. (23), λ_{max} 5.65 μ].

Anal. $C_6H_{10}O_5$ (162.2) Calc'd: C, 44.45; H, 6.22
Found : C, 44.63; H, 6.21

Synthesis of L-Streptose

Attempted Ozonolyses of 1,2-O-Isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose. A mixture of ozone in oxygen was bubbled through a solution of 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (557 mg., 2.78 mmole), anhydrous pyridine (242 mg., 3.0 mmole), and redistilled methylene chloride (70 ml.) for 7.75 min. (total ozone, 5.56 mmole) at -82°. The blue solution was immediately rapidly added with stirring to 6.63 g. of powdered zinc. The mixture was stirred for one hour at 25°. The solids were filtered and the filtrate was washed with saturated aqueous sodium bicarbonate (30 ml.) and 1 N hydrochloric acid (30 ml.). The aqueous washings were combined and extracted with three 30-ml. portions of methylene chloride. All of the methylene chloride solutions were combined, dried, and evaporated. The residue (277 mg., 50%) was a yellow syrup. The infrared spectrum (liquid film) of the product showed absorption at 2.85, 3.36, 5.65, 5.80, 6.91, and 7.30 μ, among others. The n.m.r. spectrum (25%, deuteriochloroform) of the product showed absorptions at 8.33-8.72 (at least seven partially overlapping peaks), 4.76-6.27 (a number of overlapping partly resolved multiplets and singlets), 4.33 (doublet, J = 4), 4.24 (doublet, J = 4), 3.99 (doublet, J = 4), and 0.28 τ (small singlet).

A mixture of ozone in oxygen was bubbled through a solution of 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (250 mg., 1.25 mmole) in anhydrous ethyl acetate (40 ml.) for 7.5 min. (total ozone, 3.75 mmole) at -82°. The blue solution was immediately added in one portion to a well-stirred suspension of zinc powder (4.0 g.) in anhydrous ethyl acetate (25 ml.). The mixture was stirred at room temperature for

two days at which time a few drops liberated iodine from two per cent aqueous potassium iodide. The solution was filtered and the filtrate was added in one portion to a solution of sodium iodide (1.0 g.) in anhydrous ethyl acetate (50 ml.). A solution of sodium thiosulfate pentahydrate (1.4 g.) in water (100 ml.) was added and the colorless mixture was extracted with four 500-ml. portions of chloroform. The combined extract was dried and evaporated. The residue (186 mg.) was an orange syrup. The infrared (liquid film) and n.m.r. spectra of the product were identical to those of 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose (87% yield).

A mixture of ozone in oxygen was bubbled through a solution of 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (254 mg., 1.27 mmole) in anhydrous ethyl acetate (40 ml.) for 7.5 min. (total ozone, 3.75 mmole) at -81°. A cold (0°) solution of sodium iodide (2.00 g.) in anhydrous ethyl acetate and an aqueous solution (80 ml.) of sodium thiosulfate pentahydrate (2.00 g.) were added to the blue solution. After stirring at 0° for 20 min., the solution was diluted with distilled water (50 ml.) and extracted with three 150-ml. portions of chloroform. The combined extracts were dried, evaporated, and yielded 188 mg. of colorless syrup. The infrared (liquid film) and n.m.r. (20%, deuteriochloroform) of the syrup were identical in all respects to those of 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose (86% yield).

A mixture of ozone in oxygen was bubbled through a solution of 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (202 mg., 1.01 mmole) in anhydrous ethyl acetate (50 ml.) for 10.0 min. (total ozone, 5.0 mmole) at -81°. The solution was added dropwise to a well stirred, hot (66°),

30 per cent aqueous hydrogen peroxide solution. The ethyl acetate was removed by aeration using nitrogen at 66°. The resulting aqueous solution was extracted with five 50-ml. portions of ether. Solid sodium bisulfite was added to the combined extract until bubbling ceased. The extract was dried, evaporated, and yielded 49 mg. of yellow syrup. The infrared spectrum (liquid film) of the product showed λ_{max} 2.88, 3.38, 5.75, 5.85, 6.86, and broad, unresolved absorption from 7.3 to 10.5 μ.

1,2-O-Isopropylidene-3-C-formyl-5-deoxy-β-L-lyxofuranose. A mixture of ozone in oxygen was bubbled through a solution of 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (1.005 g., 5.02 mmole) in anhydrous ethyl acetate (70.0 ml.) for 25.0 min. (total ozone, 12.5 mmole) at -80°. Dry nitrogen was bubbled through the blue solution until it was colorless. One drop of the colorless solution instantly liberated iodine from two per cent aqueous potassium iodide. The cold solution was added to a well-stirred mixture of five per cent palladium on carbon and anhydrous ethyl acetate maintained at 0° (the catalyst had been equilibrated with hydrogen at 0° before the addition). After the addition was complete, the mixture consumed 4.94 mmole (corrected to STP) of hydrogen within 27 min.; consumption then ceased. The catalyst was filtered and was washed well with anhydrous ethyl acetate. The filtrate was evaporated and the residue was dissolved in anhydrous benzene (100 ml.). The solution was evaporated and yielded 1.083 g. (107%) of colorless syrup. The product gave a strong positive Benedict's test. The n.m.r. spectrum (30%, carbon tetrachloride) of the product (obtained within one hour after preparation) showed absorption at 8.38-8.93 (6 peaks, area 19.8), 5.09-6.61 (partially resolved multiplets, area 10.5),

4.28-4.48 (4 peaks, area 2.0), and 0.33 τ (singlet, area 0.7). The integration of this spectrum was completely unsatisfactory for the expected product. The infrared spectrum (liquid film) of the product (obtained within one hour after preparation) showed λ_{max} 2.81, 3.30, 5.78, 7.25, 9.06, and 11.42 μ, among others. The freshly prepared product was soluble in carbon tetrachloride. After one day, the product was insoluble in both carbon tetrachloride and water.

A freshly prepared sample was dissolved in redistilled dioxane and centrifuged. The supernatant liquid was lyopholized. The specific rotation was $[\alpha]_D$ -16.3 ± 0.5° (c 3.99, dioxane).

Anal.	$C_9H_{14}O_5$ (202.2)	Calc'd: C, 53.46; H, 6.98
	$C_9H_{14}O_5 \cdot H_2O$ (220.2)	Calc'd: C, 49.09; H, 7.32
		Found : C, 49.77; H, 7.01
		Found : C, 49.77; H, 7.01

A freshly prepared sample (0.300 g., allowed to stand at room temperature for one day) was sublimed in vacuo using a cold water (0°) condenser. Fraction one (23-40°, 0.2 mm.) weighed 46 mg., m.p. 54-59°. Fraction two (40-50°, 0.2 mm.) weighed 13 mg., m.p. 65-68°. The n.m.r. spectrum (saturated deuteriochloroform solution) of the combined sublimate showed absorption at 8.69, 8.56, and 8.36 (doublet, J = 6.5; singlet; singlet; respectively, total 8.9H), 6.87 (1.7H, broad singlet), 5.93 (1.1H, quartet, J = 6.5), 5.38 (1.0 H*, doublet, J = 4.3), 4.23 (1.0 H, doublet, J = 4.3), and 0.25 τ (0.6H, singlet). After the n.m.r.

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* Assumed.

spectrum was determined, the solvent was evaporated, and the sublimate was resublimed. Fraction one (35-45°, 0.2 mm.) weighed 11 mg., m.p. 59.5-65.5°. Fraction two (45-90°, 0.2 mm.) weighed 13 mg., m.p. 63.5-73.5°. The residue gave a positive Benedict's test. The infrared spectrum (pellet) of fraction two was determined after two weeks and showed negligible absorption in the 5.5-6 μ region.

The elemental analysis (duplicate) of fraction two was obtained.

Anal.	$C_9H_{14}O_5$ (202.2)	Calc'd: C, 53.46; H, 6.98
	$C_9H_{14}O_5 \cdot H_2O$ (220.2)	Calc'd: C, 49.09; H, 7.32
		Found : C, 48.03; H, 7.29
		Found : C, 48.18; H, 7.28

1,2-O-Isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose. A solution of the syrupy 1,2-O-isopropylidene-3-C-formyl-5-deoxy-β-L-lyxofuranose (0.205 g., 1.24 mmole, allowed to stand for one week after preparation), sodium borohydride (0.112 g., 2.96 mmole), and absolute ethanol (40 ml.) was boiled under reflux for 1.6 hr. The cooled solution was diluted with distilled water (25 ml.) and was extracted with four 100-ml. portions of chloroform. The combined extract was dried and evaporated and yielded 138 mg. (55%) of white crystals, m.p. 103.5-106°. The product was sublimed (50-70°, 0.4 mm.) and yielded 117 mg. (46%) of white crystals, m.p. 104.5-106°, $[\alpha]_D^{26}$ +7.6 ± 0.5° (c 4.12, methanol). The infrared spectrum (pellet) was superimposable with that of 1,2-O-isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose prepared previously.

The melting point of a mixture of the product and 1,2-O-isopropyl-

idene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose (m.p. 104-106°) was 104.5-106°.

L-Streptose. A mixture of 1,2-O-isopropylidene-3-C-formyl-5-deoxy-β-L-lyxofuranose (0.659 g., 3.21 mmole), redistilled dioxane (15 ml.), distilled water (10 ml.), and Dowex 50W-X8 (H^+) (20 ml.) was stirred at room temperature for 44.0 hr. The resin was filtered and washed thoroughly with distilled water. The filtrate was concentrated to ca. 10 ml. and lyopholized. The residue (0.513 g., 89%) was a yellow glass, and was chromatographed over carbon-celite (60 g., column 43.4 cm. x 2.0 cm., flow rate 38 ml./hr.) and was eluted with distilled water (fraction volume, 70 ml.). The individual fractions were tested with Benedict's reagent before concentration to ca. 10 ml. and lyopholization. Fractions 1-5 were non-reducing and contained 10 mg. of white solid (column throw). Fractions 6-14 were reducing and contained 387 mg. (67%) of L-streptose, a colorless glass. A number of attempts were made to crystallize this material without success. Fractions 15-27 were reducing and contained an additional 58 mg. (10%) of product. Further elution of the column yielded only traces of reducing material. The specific rotation of fraction 11 was $[\alpha]_D^{23}$ (30 min.) -16.2 ± 0.7° and $[\alpha]_D^{23}$ (51 hr.) -17.7 ± 0.6° (c 3.28, water).

Paper chromatography of the compound showed only one spot (PC) in both BEW (R_F 0.59, R_G 1.90) and EAW (R_F 0.39, R_G 2.78).

The infrared spectrum (pellet) of the compound is given as Figure 17. The n.m.r. spectrum (20.5%, deuterium oxide, external DSS) of the compound is given as Figure 18.

L-Streptosonic Acid Monolactone. A mixture of L-streptose (0.532

g., 2.95 mmole, not chromatographed), anhydrous strontium carbonate (2.10 g.), distilled water (50 ml.), and bromine (2.10 g., 13.1 mmole) was allowed to stand at room temperature, in the dark, for 5.0 hr. The product was isolated as previously described* (except that 2.50 g. of silver carbonate was used). The residue from lyopholization was triturated with three 20-ml. portions of redistilled 2-butanone. The insoluble material (1.471 g.) was dried *in vacuo* at room temperature and then dissolved in distilled water (50 ml.). After Dowex 50W-X8 (H^+) (30 ml.) was added, the mixture was stirred at room temperature overnight. The resin was filtered and washed thoroughly with distilled water. The filtrate was concentrated to *ca.* 10 ml. and lyopholized. The residue (0.822 g.) was triturated with boiling, redistilled 2-butanone (25 ml.) and the solids were removed by centrifugation. The supernatant liquid was concentrated to *ca.* 2 ml. and chloroform (10 ml.) was added. The solids were removed by centrifugation and the supernatant liquid was evaporated. The residue was decolorized using anhydrous methanol (20 ml.) and Darco G-60 (0.3 g.). To remove traces of water, a solution of the residue in anhydrous acetone (10 ml.) and anhydrous benzene (50 ml.) was evaporated. The drying was repeated. After further drying *in vacuo* at room temperature, the residue weighed 265 mg. (51%).** The residue was dissolved in redistilled 2-butanone (0.5 ml.) and chloroform (12 ml.) was added. After cooling overnight in the refrigerator, 39 mg. (7.5%) of white crystals was obtained. After thorough

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* See page 68, this thesis.

** The n.m.r. spectrum of this material and that of the final crystalline product were identical.

drying *in vacuo* at 50°, the product showed m.p. 154-156°, $[\alpha]_D^{26}$ -41.1 ± 2.0° (*c* 0.975, water) [lit. (62), m.p. 146-148°, $[\alpha]_D^{25}$ -37° (*c* 0.7, water)].

Anal.	$C_6H_8O_6$	Calc'd: C, 40.92; H, 4.58
	(176.1)	Found : C, 40.88; H, 4.64

The infrared spectrum (pellet) of the compound is given as Figure 19. The n.m.r. spectrum (16%, acetone-D_6) of the compound showed absorption at 8.67 (3H, doublet, *J* = 6.5), 5.16 (1H, quartet, *J* = 6.6), 5.05 (1H, singlet), and 3.85 τ (3H, singlet). The absorption position of the latter peak was concentration dependent (2.90 τ at 40%).

A sample* of syrupy L-streptosonic acid monolactone (320 mg.), prepared as described elsewhere (62) from streptomycin was dried as described above and was crystallized from redistilled 2-butanone and chloroform. The compound was recrystallized, dried thoroughly (yield, 52 mg.) and showed m.p. 154.5-156.5°, $[\alpha]_D^{26}$ -40.8 ± 1.8° (*c* 1.002, water). The infrared spectrum (pellet) of the compound is given as Figure 20. The n.m.r. spectrum (21%, acetone-D_6) of the compound showed absorption at 8.67 (3H, doublet, *J* = 6.5), 5.13 (1H, quartet, *J* = 6.5), 5.03 (1H, singlet), and 3.44 τ (3H, broad singlet).

The melting point of a mixture of authentic and synthetic L-streptosonic acid lactone was 153.5-155.5°.

Reaction of 1,2-O-Isopropylidene-3-C-formyl-5-deoxy-β-L-lyxofuranose with Alkali. A solution of syrupy 1,2-O-isopropylidene-3-C-formyl-5-deoxy-β-L-lyxofuranose (15.2 mg.) in aqueous 1.0 N sodium

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* The author is very grateful to Mr. R. K. Chawla for this sample.

hydroxide (5 ml.) was maintained at 100° for 15 min. The solution was cooled and a few drops were added to 0.5 ml. of an aqueous solution of ferric ammonium sulfate (1%) and sulfuric acid (0.75 N). A purple-red solution resulted.

A solution of L-streptose (21.8 mg.) in aqueous 1.0 N sodium hydroxide (10 ml.) was maintained at 100° for 15 min. When the cooled solution was treated as described above, no color was observed. No color was observed when the solution was heated for an additional 30 min., cooled, and tested.

CHAPTER III

DISCUSSION OF RESULTS

The purpose of this research was to accomplish a definitive synthesis of 3-C-formyl-5-deoxy-L-lyxose, the structural formula assigned to streptose. In addition to completing the synthetic proof of the structures of the three component fragments of streptomycin, such a synthesis would make possible a plan of the total synthesis of streptomycin.

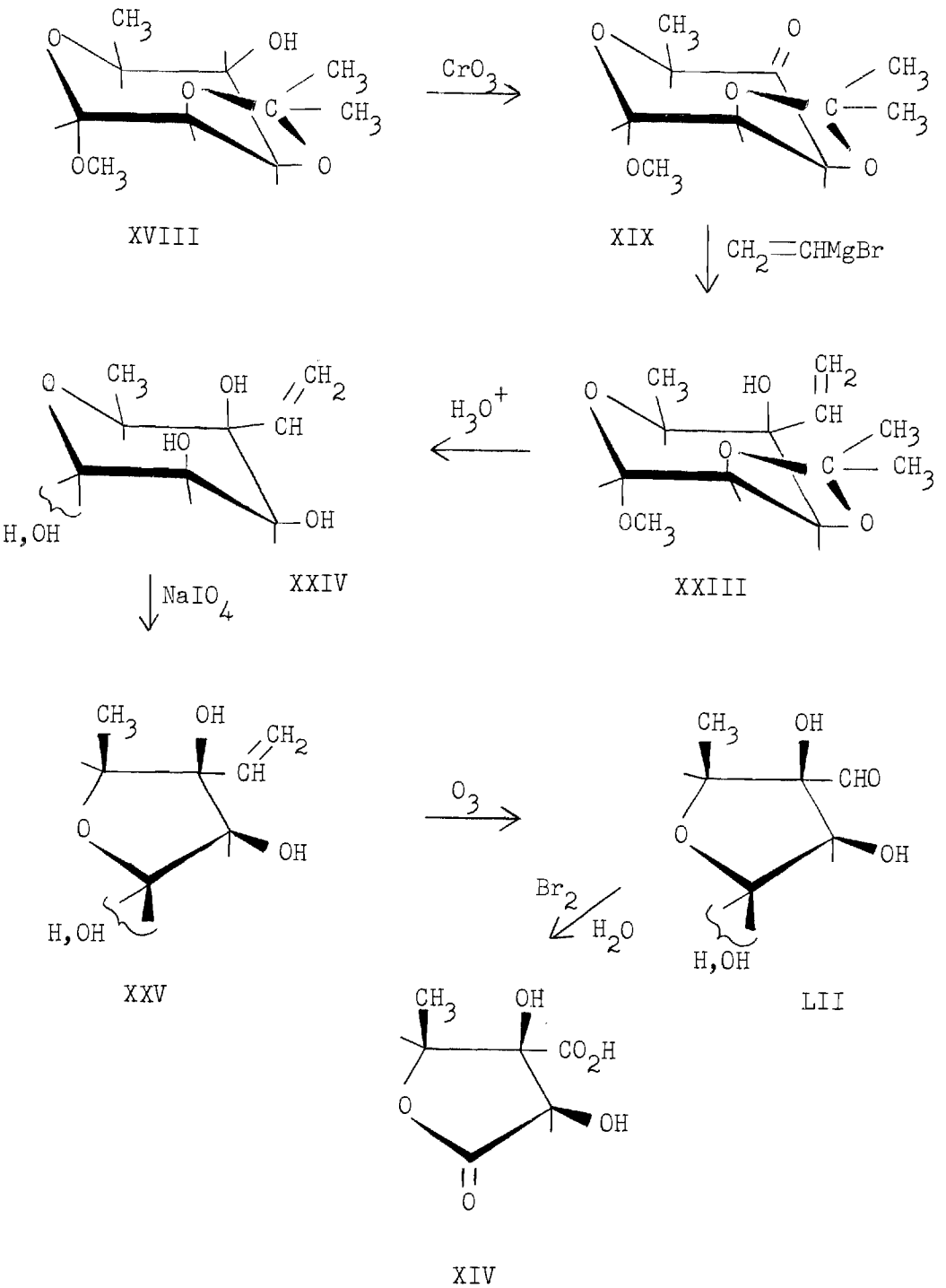
A definitive synthesis of streptose must involve either reactants of known stereochemistry, stereospecific reactions, or a combination of both. Furthermore, the reactions performed upon non-asymmetric centers must either not alter the asymmetry of other portions of the molecule or must change it in a known, predictable way. The synthesis of previously unknown compounds must be accompanied by thorough characterization.

The extensive use of nuclear magnetic resonance spectroscopy as an aid in structure proof was planned. This technique affords a particularly fine method for the determination of structural changes within a series of structurally similar compounds. The application of well documented reactions was planned as the only meaningful synthetic approach.

The L-Rhamnose Approach

A proposed synthesis of streptose starting from the known compound, methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (XVIII), is shown as Chart 1.

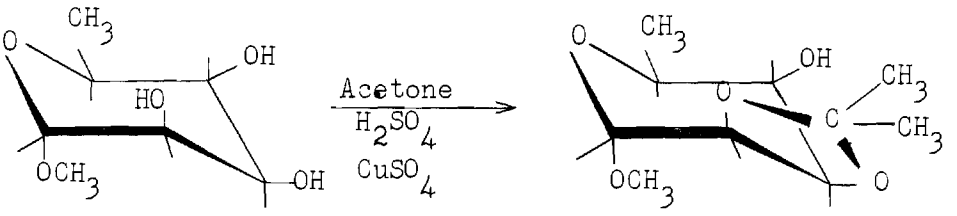
Chart 1. The L-Rhamnose Approach to the Synthesis of L-Streptose.



Methanolysis of L-rhamnose was performed according to the method of Levene and Muskat (41) and gave an essentially quantitative yield of a nonreducing mixture of methyl α- and methyl β-L-rhamnopyranoside. The product could be distilled *in vacuo*; however, the yield was lowered considerably (to 70%) because of the partial decomposition of the compounds at the required pot temperature. The α and β anomers of methyl L-rhamnoside have been separated by crystallization and the physical constants for each have been reported (41). Based on the observed specific rotation of the mixture obtained and reported rotations for each anomer, the product contained 90 per cent of the α and 10 per cent of the β anomer. GLC analysis of the mixture showed two partially overlapping peaks that had relative areas of 1:19. The GLC analysis of carbohydrates has been investigated thoroughly and is probably the most accurate method for the determination of the composition of anomeric mixtures (64,65). Because of the great predominance of the α anomer, no attempt was made to separate the isomers. The n.m.r. spectrum of the mixture was not structurally definitive. The doublet (J = 6) at 8.74 τ is assigned to the terminal methyl group and the sharp singlet at 6.68 τ is assigned to the glycosidic methyl group.

The reaction of the mixture of anomeric methyl rhamnopyranosides with acetone to give the 2,3-O-isopropylidene derivative was performed as previously described (40,41). The placement of the isopropylidene group has been proved by degradation (41). Since the reaction involves an equilibrium with water, it is essential that anhydrous acetone be used. Reactions performed without this precaution gave considerable amounts of recovered starting material. Vacuum distillation using a

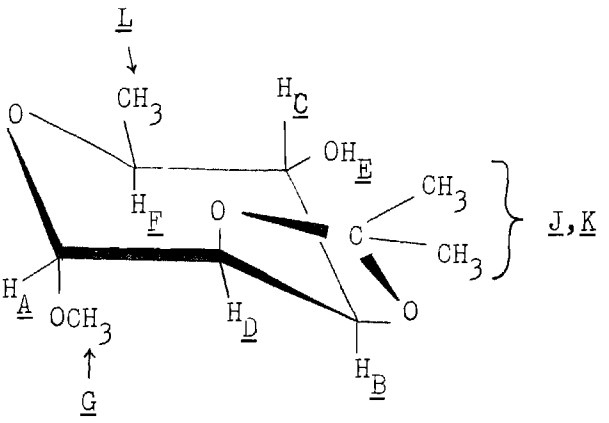
6 in. Vigreux column did not remove the starting material present (as indicated by paper chromatographic analysis) and, although the yield was



XVIII

less, the product was best purified by distillation using a spinning band distillation column. Paper chromatography of product purified in this manner did not reveal any methyl rhamnosides. GLC analysis of the product showed two peaks with relative areas of 1:83. Because of the very small amount (1.2%) of the β isomer present, the product hereafter will be referred to as methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (XVIII). Since the optical rotation of the product is more negative (-24.6° versus -14.1°) than the values reported in the literature for anomeric mixtures of unknown composition (41,44), it is presumed that the spinning band fractional distillation removed most of the probably more volatile β anomer (66) that was present. The other physical constants measured are in reasonable agreement with those reported in the literature. All of the absorptions present in the n.m.r. spectrum of the compound can be assigned, as shown below, and the spectrum is completely consistent with the structural formula.

Prior to the start of this research, the literature contained very few examples of the oxidation of carbohydrate cyclic secondary alcohol groups to ketones (67). A likely reagent that had not been ap-



XVIII

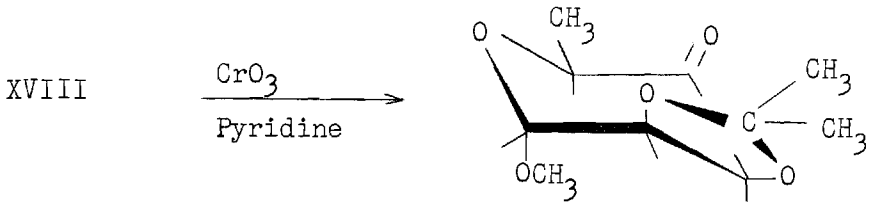
H	τ	J, cps
A	5.30	AD = 0
B	6.01	BC = 0
C	6.04	BD = 5.9
D	6.15	CF = 0
E	6.44	FL = 6.0
F	6.61	
G	6.72	
J	8.54	
K	8.71	
L	8.79	

applied to this problem was the chromium trioxide-pyridine complex (45). Using this reagent, the oxidation of steroidal cyclic secondary alcohols had been effected with excellent yields (45,68). A single example of the oxidation of a carbohydrate acyclic secondary alcohol (73% yield) with this reagent had been reported (69). The apparent inability of the reagent to attack olefins and other easily oxidized groups (45,68), as well as the basicity of the medium (methyl glycosides and isopropylidene groups are not removed by pyridine) made the investigation of this reagent very attractive.

Apparently these observations were not unique since during the course of this research several reports of the use of this reagent have appeared (70,71,72). Although no experimental details have been published,

the yields were reported to vary between 35 and 60 per cent for the oxidation of cyclic (pyranoside) secondary hydroxyl groups (72).

The oxidation of XVIII to methyl 2,3-isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose (XIX) using the chromium trioxide-pyridine complex was studied extensively. During this investigation 26 individual



XIX

reactions were performed. The results of certain representative reactions are shown in Table 1 and Table 2.*

The recovery of material from the reaction varied considerably when different isolation procedures were used. The reduction in yield when procedure A or B was used was probably due to the rapid hydrolysis of the isopropylidene group in 2 N hydrochloric acid (the hydrolyzed material would not be expected to be soluble in chloroform). Longer reaction time intervals and higher temperatures caused general decomposition, as evidenced by the infrared spectra of the crude product, and consequently poorer recoveries. The variation in yield for essentially

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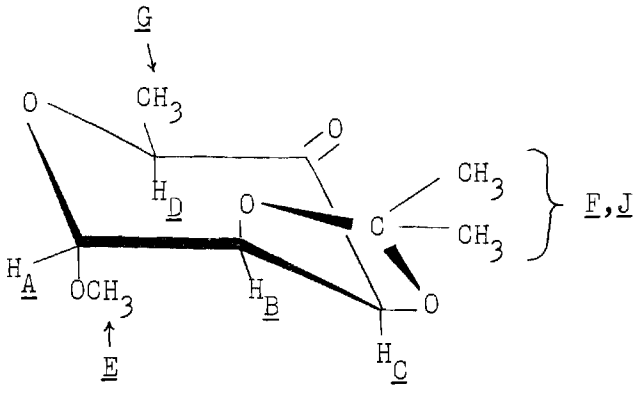
* Pages 18 and 21, this thesis.

identical reactions using isolation procedure E was probably due to variations in the time required to remove the pyridine at 45°.

The removal of small amounts of chromium oxides present in the crude product had to be accomplished immediately. This was best effected by silicic acid chromatography. If the product was allowed to stand for two weeks before chromatography, approximately 25 per cent yield (based on the recovered material) of maltol (2-methyl-3-hydroxy-4(H)-γ-pyrone) was obtained. This material was identified by a comparison of its ultraviolet, infrared, and n.m.r. spectra, color tests, and melting point with those of an authentic sample (no depression of melting point when mixed with the maltol obtained above). The exact source of this material was not clear at first; however, recent studies in these laboratories have indicated that maltol is formed in good yield from XIX by means of acid catalysis (73). Maltol has been reported as a degradation product of many carbohydrate materials in addition to streptomycin (11,74).

Since immediate chromatography efficiently separated the starting material from the desired product, mild reaction conditions were chosen that gave a high recovery and a moderate yield. The purified product

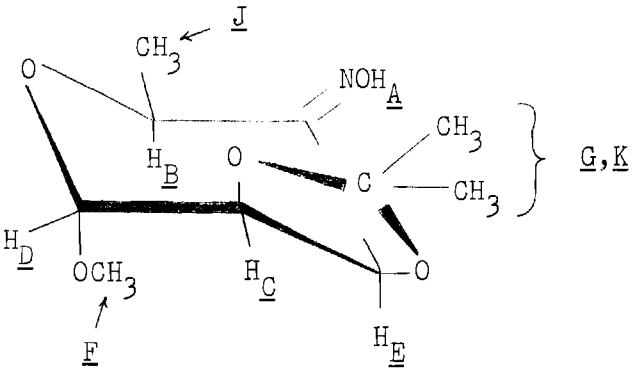


XIX

H	τ	J, cps
A	5.15	AB = 0
B	5.56	BC = 0
C	5.56	DG = 6.9
D	5.74	
E	6.53	
F	8.51	
G	8.60	
J	8.63	

exhibited satisfactory infrared and n.m.r. spectra and showed only one peak when analyzed by GLC.

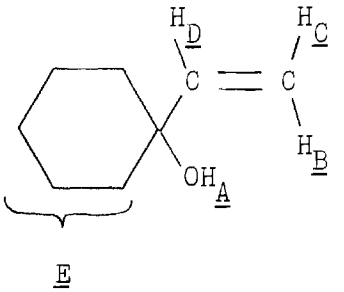
Compound XIX was further characterized by means of a crystalline oxime derivative (XX). The elemental analysis of XX was satisfactory and the infrared and n.m.r. spectra of the compound were completely consistent with the structural formula.



XX

H	τ	J, cps
A	0.83	BJ = 6.7
B	5.09	CD = 0
C	5.22	CE = 7.6
D	5.35	
E	5.72	
F	6.57	
G	8.43	
J	8.48	
K	8.63	

1-Vinylcyclohexanol (XXI) was prepared as a model compound for both the Grignard reaction and subsequent transformations involving vinyl carbohydrates. The vinyl magnesium chloride that was used was purchased and contained such a large amount of vinyl polymer that it was deemed useful only for the preparation of XXI, which could be easily distilled from the polymeric material. The properties of XXI were in agreement with those reported in the literature. The infrared and n.m.r. spectra were consistent with the structural formula of XXI and indicated the type of vinyl absorption to be expected. The n.m.r. spectrum of the vinyl protons was analyzed (75) and the results of this analysis are shown below.

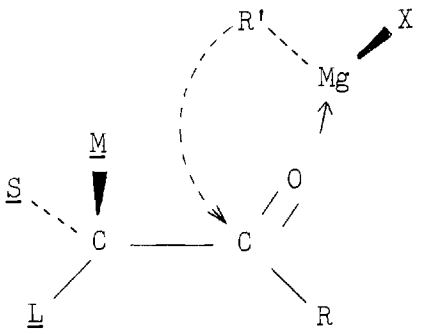


H	τ	J, cps
A	4.13	BC = - 2.2
B	4.74	BD = 17.6
C	5.02	CD = 10.4
D	5.97	
E	8.47	

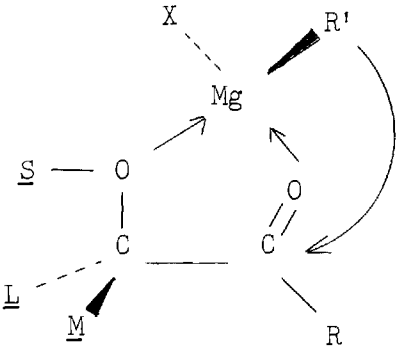
XXI

The addition of Grignard reagents to unsymmetrical carbonyl compounds has been studied extensively (76,77). In acyclic compounds, the fact that the reagent has been shown to add preferentially to the less sterically hindered side of the carbonyl group is known as Cram's Rule (shown at the left below) (78). However, the presence of atoms (oxygen, nitrogen) on asymmetric centers adjacent to the carbonyl group that can complex with the Grignard reagent and give a cyclic intermediate can affect the stereochemical result of the reaction. In these instances a different, cyclic model (shown at the right below) must be used in order to predict the stereochemistry of the product. Cram's models for both situations are shown below (76,77), where L is the largest group (the largest relative steric bulk at the attachment atom), M is the next largest group, and S is the smallest group.

Grignard additions to carbohydrate carbonyl compounds are well known and, as expected, do not cause either the hydrolysis or epimerization of acetal and glycoside groups (69,79). Wolfrom and Hanessian showed that the addition of methylmagnesium iodide to the acyclic carbonyl group of 3-O-benzyl-1,2-O-isopropylidene-α-D-xylo-pentodialdo-1,4-furanose



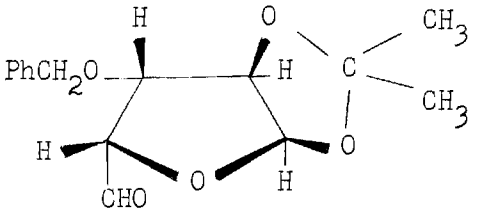
Acyclic Addition



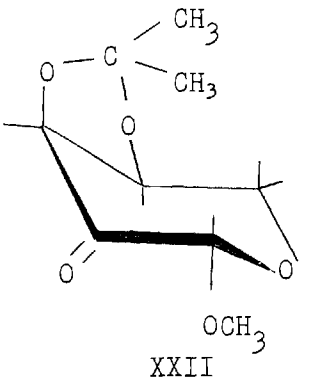
Cyclic Addition

Cram's Models

(shown below) gave only the product predicted by the cyclic model (80). They also observed the same type of addition with 1,2-O-isopropylidene-3-O-benzyl-6-deoxy-α-D-xylo-hexofuranos-5-ulose (81). In both of these instances the carbonyl group was not cyclic.



Recently, Overend and co-workers have shown that Grignard additions to methyl 3,4-O-isopropylidene-β-L-erythro-pentopyranos-2-ulose (XXII) gave only the arabino configuration (except for methylmagnesium



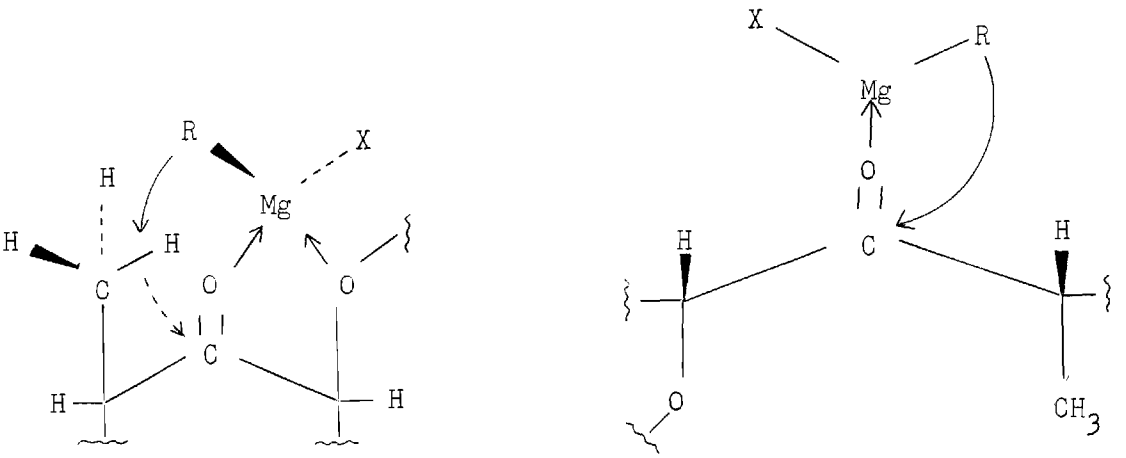
XXII

iodide, for which a "very small amount" of the ribo isomer was obtained) (70,72,82). In this instance Cram's models are not very helpful, since the possibility of the formation of cyclic complex intermediates exists for both sides of the carbonyl group and one side of the carbonyl group is definitely more sterically hindered than the other. Because the products are not those predicted by the non-cyclic model, complex formation must be responsible. Exactly why one side would complex while the other, less sterically hindered side would not, is not clear.

The situation is less confusing for the compound studied herein. An inspection of molecular models reveals that the possibility of complex intermediate formation exists for only one side of the carbonyl group of XIX. However, the decomposition of such a complex to give a product that has the manno configuration is not favored because of steric interaction with the methyl group on the adjacent atom as shown.

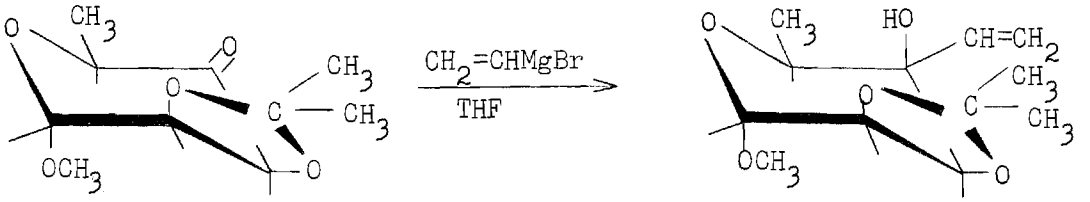
While the other side of the carbonyl group offers no possibility for complex formation, there are no bulky groups present that would interfere with the addition. On this basis it is expected that, while both isomers may result, the one that has the talo configuration should

predominate.



Possible XIX - Grignard reagent reactions

The vinyl Grignard reagent was prepared as described previously (83). In order to obtain crystalline methyl 2,3-O-isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside (XXIII), a completely anhydrous solution of freshly prepared XIX in tetrahydrofuran was necessary. Attempts to



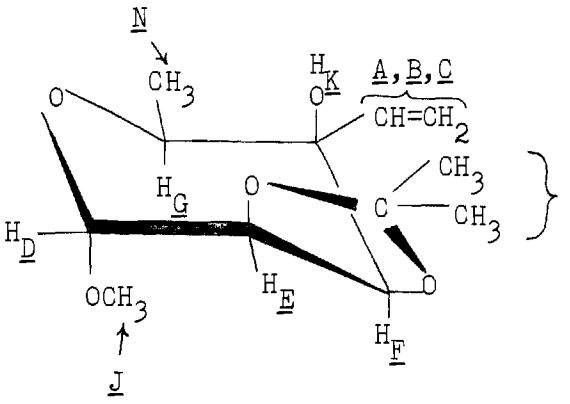
XIX XXIII

hydrolyze the Grignard adduct with hydrochloric acid or ammonium chloride gave very little ether-soluble material, presumably because of the rapid

hydrolysis of the isopropylidene group. When water was the hydrolysis medium there was obtained a 104 per cent yield of yellow syrup (the higher-than-the theoretical yield is probably due to the formation of vinyl polymer during the reaction), which after chromatography and sublimation gave a 49 per cent yield of crystalline material. GLC analysis of the purified material showed only one symmetrical peak. Integration of the GLC analysis of the crude product indicated (if all constituents were volatile) the presence of 66.5 per cent of the purified material. The presence of many peaks in the GLC analysis of the crude product makes it difficult to eliminate the possibility of the presence of the manno isomer. However, the n.m.r. spectra of all of the silicic acid chromatography fractions and the sublimation residue indicated that the principal impurities were probably vinyl polymers.

The fact that the product was eluted from silicic acid in the second and third column volumes of chloroform rather than the fourth through the sixth column volumes, as was observed for XVIII, indicates that XXIII is less polar or is less able to hydrogen bond to the polar adsorbant than XVIII (84). This behavior is consistent with that expected for the talo configuration because the hydroxyl group of XXIII would be more sterically hindered in this configuration and therefore less able to interact with the adsorbant. The manno configuration of XXIII would be expected to have adsorption properties similar to XVIII (which has the manno configuration).

The elemental analysis of XXIII was satisfactory for the expected structure. The infrared and n.m.r. spectra were also consistent with the structure assigned.

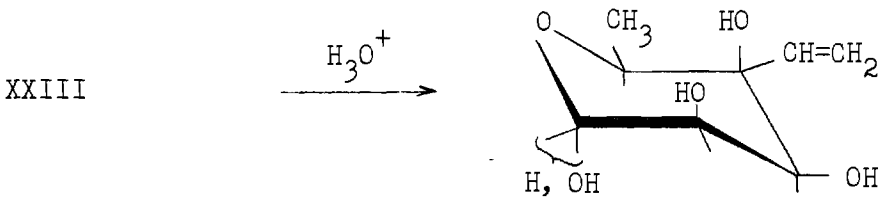


H	τ	J, cps
A, B, C	4.06-4.88	(not analyzed)
D	5.03	DE = 0
E, F	5.89	GN = 6.7
G	6.24	
J	6.60	
K	7.55	
L	8.41	
M	8.63	
N	8.82	

XXIII

The next reaction in the proposed synthetic sequence (Chart 1) is the acid catalyzed hydrolysis of XXIII to give 3-C-vinyl-6-deoxy-L-talose (XXIV). This compound would be expected to react preferentially with one mole of periodate and give 3-C-vinyl-5-deoxy-L-lyxose (XXV). Sodium periodate has been shown to react fastest with the C_1-C_2 glycol grouping of carbohydrates (85).

Compound XVIII and 1-vinylcyclohexanol were chosen as models for the acid hydrolysis of XXIII. Although the hydrolytic removal of the

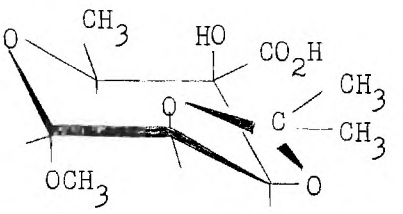


XXIV

isopropylidene group was expected to be rapid, the methyl glycoside function was expected to be removed more slowly. Since XXIII is a tertiary allylic alcohol, acids might cause rearrangement, dehydration, or isomerization. The criterion chosen was that the conditions necessary to effect the hydrolysis of both protecting groups of XVIII must not alter in any way the structure of XXI.

It was observed that 1 N hydrochloric acid at either room temperature or at 50-55° and Dowex 50W-X8 (H^+) at room temperature caused drastic changes in the n.m.r. spectrum of XXI. In all of the experiments performed, the length of time that was required for the alteration of XXI was less than that required for the hydrolysis of the protecting groups of XVIII.

Since it was clearly indicated that the hydrolysis of XXIII would not proceed as required, this approach to the synthesis of streptose was abandoned. Several attempts were made to oxidize XXIII to the corresponding carboxylic acid, which would be expected to be more stable to acid hydrolysis, without success.

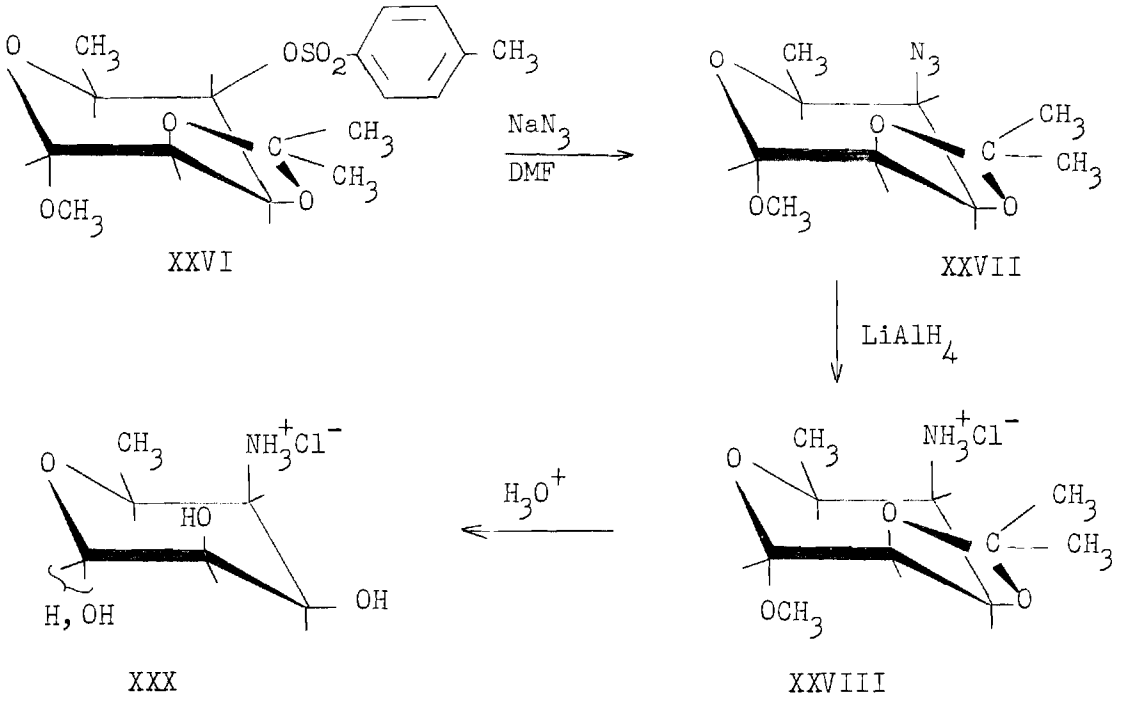
XXIII $\xrightarrow{[Ox]}$ 

The chemistry of the amino sugars is one of the most rapidly developing areas of carbohydrate research (72,86). In the past few years many new amino sugars have been isolated from a variety of antibiotics,

lipopolysaccharides, and other natural products (72,86,87). The characterization and synthesis of these unusual compounds have required the application (and development) of relatively new organic reactions and procedures (72).

The first example of the isolation of a 4-amino-4,6-dideoxy-hexose from a natural product was reported recently (88). Initial studies indicated that the sugar possessed the L-erythro configuration at C_4-C_5 (88). During the course of the following research, it was determined by synthesis that the new amino sugar (viosamine) was 4-amino-4,6-dideoxy-D-glucose (89,90,91).

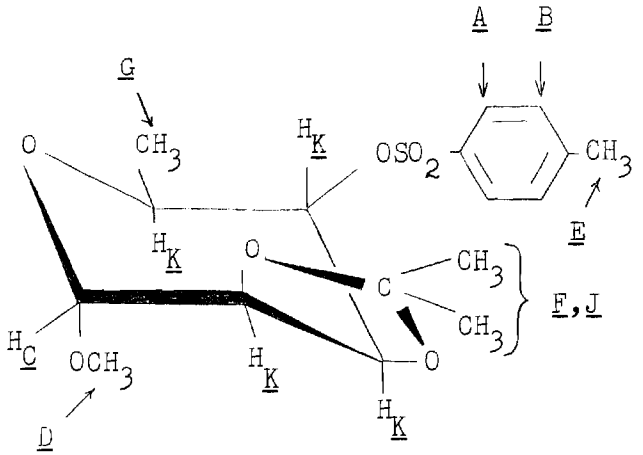
Because of the growing importance of these unusual sugars, the synthesis of another 4-amino-4,6-dideoxyhexose appeared desirable. The khown tosylate of XVIII (41,44) could probably be easily converted into 4-amino-4,6-dideoxy-L-talose by the synthetic sequence shown below.



XXVI XXVII XXVIII XXX

Another L-talo amino sugar, 2-amino-2,6-dideoxy-L-talose (pneumosamine) has been isolated recently (92).

Methyl 2,3-O-isopropylidene-4-O-(p-toluenesulfonyl)-α-L-rhamnopyranoside (XXVI) was prepared essentially as described previously (41). The observed properties of the product were in accord with those reported in the literature (40,44). The purity of XXVI was assayed by GLC analysis, which showed only one peak (at a much greater R.T. than XVIII). The infrared and n.m.r. spectra of XXVI were consistent with the structural formula. The introduction of the p-toluenesulfonyl group caused several changes in the n.m.r. absorptions of the ring hydrogen atoms. These changes result in a complex pattern of partly resolved absorption between 5.94 and 6.49 τ, which cannot be assigned with any certainty. The other absorptions are assigned below.



XXVI

H	τ	J, cps
A	2.26	AB = 10
B	2.78	GK = 7
C	5.28	
D	6.71	
E	7.59	
F	8.58	
G	8.72	
J	8.81	
K	----	

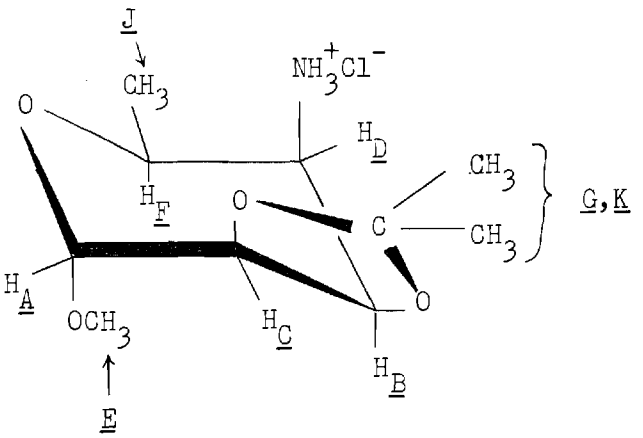
The displacement of carbohydrate p-toluenesulfonate and methanesulfonate groups by azide ion (N_3^-) as well as other nucleophilic agents

in N,N-dimethylformamide (DMF) is well known to be accompanied by the inversion of the configuration at the reaction center (93-95). In several instances, the inversion has been proved by degradation of the product to known compounds (95-98).

The displacement of the p-toluenesulfonate group of XXVI by azide in boiling DMF was performed according to the procedure of Reist et al. (99) and gave an 82 per cent yield of syrupy methyl 2,3-O-isopropylidene-4-azido-4,6-dideoxy-α-L-talopyranoside (XXVII). The product exhibited the expected azido group absorption (4.72 μ) in the infrared region and showed no absorption due to hydroxyl, p-toluenesulfonyl groups, or residual DMF. The reduction of the azido group of XXVII was effected using lithium aluminum hydride according to the procedure of Bose et al. (98). The crystalline methyl 2,3-O-isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranoside hydrochloride (XXVIII) was obtained in 27.5 per cent overall yield from XXVI. The elemental analysis and infrared spectrum of XXVIII were consistent with the structural formula. Paper chromatography of XXVIII indicated the presence of only one compound. When aqueous solutions of XXVIII were allowed to stand at room temperature for several weeks, paper chromatography showed two more spots (faint), which were presumably due to methyl 4-amino-4,6-dideoxy-α-L-talopyranoside hydrochloride and 4-amino-4,6-dideoxy-L-talose hydrochloride.

The n.m.r. spectrum of XXVIII (shown in Figure 3) was exceptionally well defined and since every absorption could be unequivocally assigned, provided further proof for the talo configuration of the product. This spectrum will be discussed more fully in a later section.

Compound XXVIII was further characterized by means of a crystalline

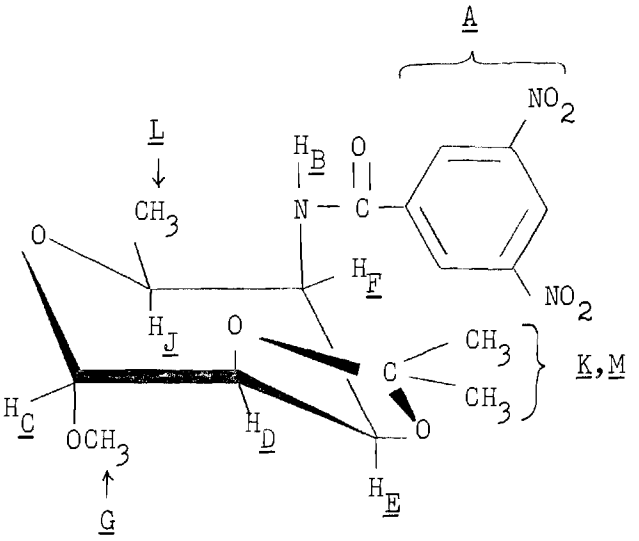


H	τ	J, cps
A	4.87	AC = 0
B	5.13	BC = 6.1
C	5.26	BD = 1.4
D	5.91	DF = 11.0
E	6.56	FJ = 6.8
F	6.62	
G	8.48	
J	8.62	
K	8.63	
(HOD	5.42)	

XXVIII

3,5-dinitrobenzoyl derivative. The elemental analysis and infrared and n.m.r (shown as Figure 4) spectra of methyl 2,3-O-isopropylidene-4-C-(3,5-dinitrobenzamido)-4,6-dideoxy-α-L-talopyranoside (XXIX) were all consistent with the structural formula. However, because of the indistinct nature of the overlapping multiplets in the 5.3-5.5 τ region, the assignments of the absorption of the C_2, C_3, and C_4 hydrogens are not definite.

The hydrolysis of the methyl and isopropylidene protecting groups of XXVIII was not expected to proceed easily since similar hydrolyses described previously had failed (89,99). However, it was hoped that careful carbon-celite chromatography of the hydrolysate would yield a small amount of pure 4-amino-4,6-dideoxy-L-talose hydrochloride (XXX). The hydrolysis conditions chosen were known to remove the protecting groups of XVIII. There was obtained after chromatography a very poor yield of a mixture of at least three ninhydrin positive compounds (as



H	τ	J, cps
A(3)*	0.82-0.98	
B	2.02	BF = 8.9**
C	4.85	JL = 7.0
D	5.39	
E	5.39	
F	5.46	
G	6.31	
J	6.38	
K	8.51	
L	8.64	
M	8.71	

XXIX

indicated by paper chromatography).

In a similar instance described in the literature, the hydrolysis of the N-acetate of a similarly protected 4-amino sugar gave the unprotected compound where the hydrolysis of the unacetylated material did not (89). In order to attempt a similar hydrolysis, methyl 2,3-O-isopropylidene-4-acetamido-4,6-dideoxy-α-L-talopyranoside (XXXI) was prepared. After silicic acid chromatography, compound XXXI was obtained as a syrup that resisted crystallization. The infrared and n.m.r. spectra of XXXI were consistent with the structural formula. When subjected to acid hydrolysis, compound XXXI gave, after careful chromatography over Dowex 50W-X8 (H^+), a poor yield of a mixture of crystals and orange

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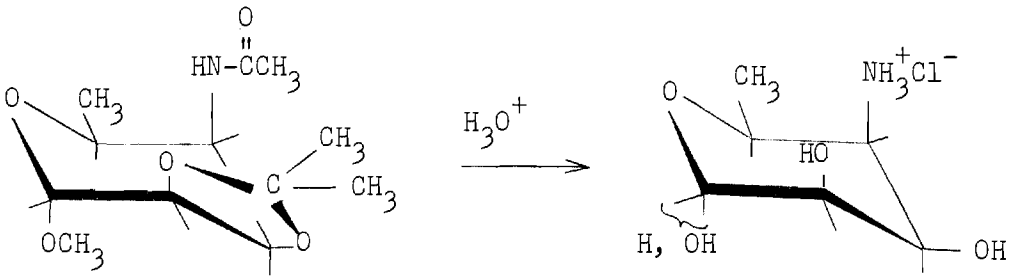
* Not analyzed.

** The fact that the B proton absorbs as two peaks may be due to restricted rotation rather than BF coupling.



XXXI XXX

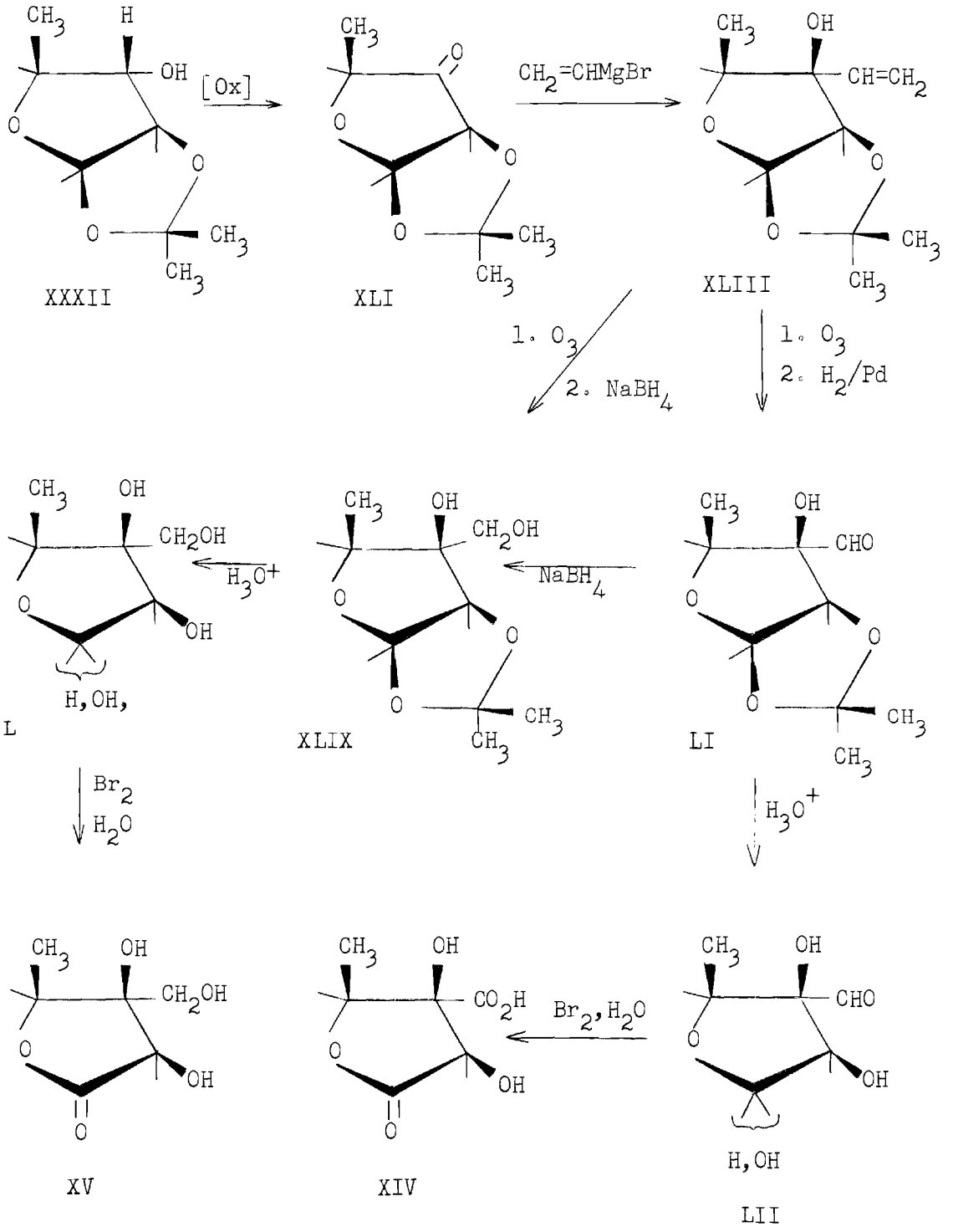
syrup. Paper chromatography of the product showed a spot at about the same R_F as was observed for aged aqueous solutions of XXVIII. Since the product showed positive ninhydrin and Benedict's tests, the hydrolysis was at least partly successful. Numerous attempts to purify the product by crystallization failed. Solutions of XXX were not stable, probably because of cyclization involving the potential aldehyde group and the amino group. When all samples no longer gave positive Benedict's tests, it was assumed that decomposition was complete.

Because only a small amount of XXVIII remained after these hydrolysis reactions, no further attempt to obtain more XXX was made. It is hoped that this compound will be characterized more fully by other workers.

The 5-Deoxy-L-arabinose Approach

This synthetic pathway to L-streptose started from the known 1,2-O-isopropylidene-5-deoxy-L-arabinofuranose (XXXII) as shown in Chart 2. Although XXXII had been prepared previously by two different sequences

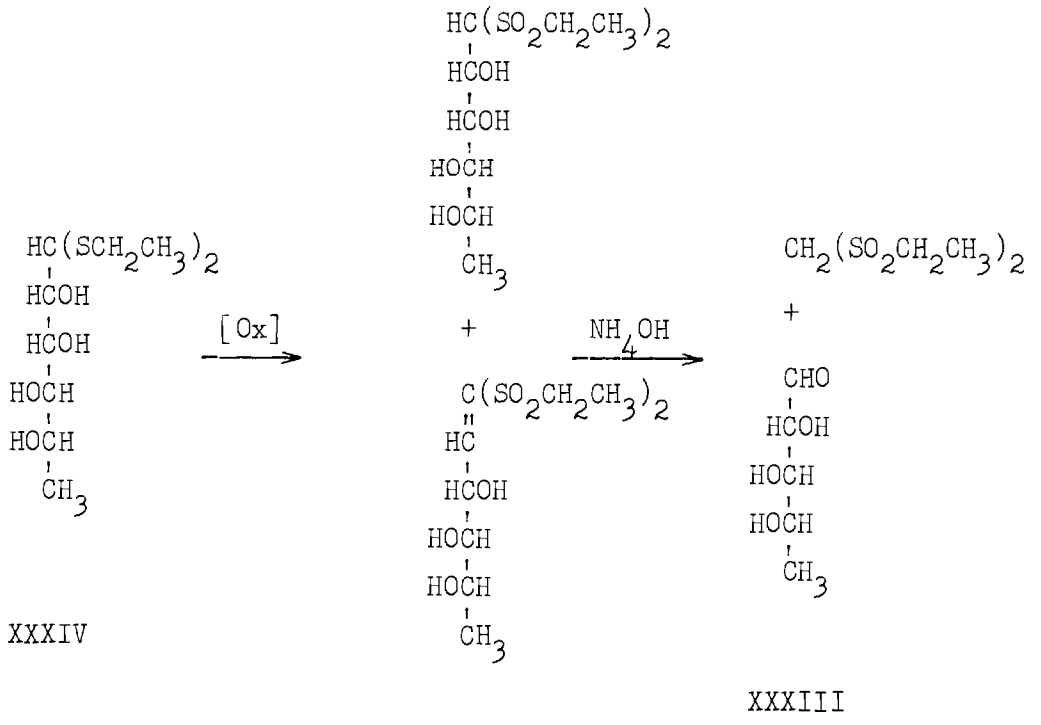
Chart 2. The 5-Deoxy-L-arabinose Approach to the Synthesis of L-Streptose and L-Dihydrostreptose.



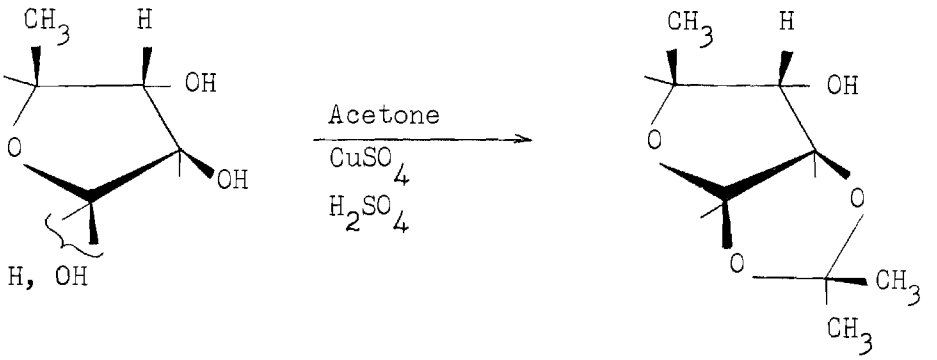
of reactions, neither seemed applicable primarily because of their length (55,56). Instead, the preparation of XXXII by the direct acetonation of 5-deoxy-L-arabinose was attempted.

5-Deoxy-L-arabinose (XXXIII) has been known since 1896, when Fischer degraded L-rhamnose by the classical method of Wohl (100). Compound XXXIII has also been prepared in many ways by a number of workers (101-106). Hough and Taylor have degraded L-rhamnose to XXXIII by the method of MacDonald and Fischer (53,107). Since a convenient preparation of the required peroxypropionic acid was available (50), the latter method, which was reported to proceed in higher yield, was chosen.

L-Rhamnose diethyl dithioacetal (XXXIV) was prepared by a modification of the method of Fischer (48). The physical properties of the product were in agreement with those recorded. The oxidation of the



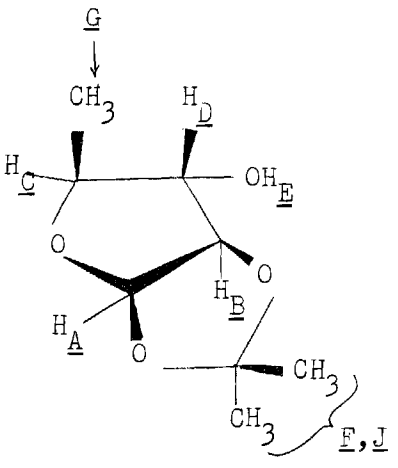
thioethyl groups did not occur as had been previously described (53). For this reaction, aqueous 4 M peroxypropionic acid was used, whereas in the earlier description, the reagent was almost anhydrous (53). Probably because of this difference, evaporation of the reaction solution gave a mixture of 1-deoxy-1,1-bis(ethanesulfonyl)-L-rhamnose and 1,1-bis(ethanesulfonyl)-L-arabino-trihydroxyhex-1-ene rather than only the first compound. That the physical properties (melting point and specific rotation) of the product were not reproducible is probably due to slight variation in the rate of addition of the peracid solution (thus causing variation in the reaction temperature). However, the properties of the product were consistent for mixtures of the two previously known products. The hydrolysis of the mixture was accomplished readily and gave an almost quantitative yield of bis(ethanesulfonyl)methane. As has been previously reported by many workers, the orange syrupy XXXIII could not be crystallized (101-106). The pentose upon direct acetonation gave, after purification, crystalline 1,2-O-isopropylidene-5-deoxy-L-arabinofuranose (XXXII). Because the acetonation reaction is an equilibrium reaction that involves water,



XXXIII XXXII

thorough drying of all reagents was essential. Even with this precaution, direct chromatographic separation indicated that the equilibrium mixture contained about 35 mole per cent of XXXII. The most convenient isolation of XXXII involved trituration of the acetonation residue with ether (to remove unreacted XXXIII), followed by evaporation of the extracts and trituration of the residue with hot ligroine. Upon cooling, cream colored crystals of XXXII were obtained that were chromatographically homogeneous (GLC). The syrupy residues could be reacetonated and finally chromatographed and gave additional amounts of XXXII. In this manner the best overall yield of XXXII from XXXIV was 45 per cent.

The observed physical properties of XXXII agreed with those given in the literature. In addition, the infrared and n.m.r. (given as Figure 5) spectra were consistent with the structural formula. The n.m.r. spectrum in particular was well defined. It is expected that the 1,2-O-isopropylidene group would be cis oriented (the β anomeric configuration)

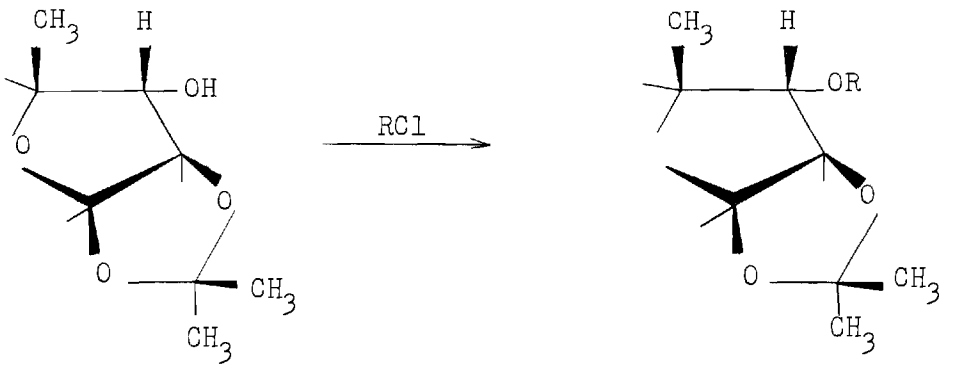


XXXII

H	τ	J, cps
A	4.12	AB = 4.1
B	5.47	BD = 0
C	5.95	CD = 2.6
D	5.96	CG = 6.8
E	6.34	
F	8.47	
G	8.61	
J	8.68	

because of the ring strain inherent in a trans fusion between two five-membered rings. The magnitude of the C_1-H, C_2-H spin-spin coupling constant (4.1 cps) provides additional evidence for the cis fusion and the β configuration. In a series of 13 similar 1,2-O-isopropylidene-furanoses, the C_1-H, C_2-H coupling constant was observed to vary from 3.5 to 3.8 cps (108). While no data are available for a similar trans fused system (perhaps an indication of the strain that would be present), the analogous coupling constant for such a compound would be expected to be much larger than observed (108). For these reasons compound XXXII is assigned the β configuration and is correctly named 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose.

The structure of XXXII has not been proved by degradation (55,56). However, the absolute stereochemistry at C_2, C_3, and C_4 was assigned by the fact that mercaptolysis of XXXII was shown to give in good yield



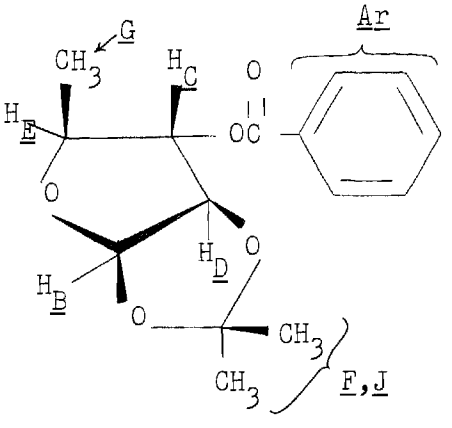
XXXII

XXXV, R = benzoyl
XXXVI, R = 3,5-dinitrobenzoyl
XXXVII, R = p-toluenesulfonyl

5-deoxy-L-arabinose diethyl dithioacetal (55). While the structure given is the only reasonable one on the basis of the earlier transformations, it seemed desirable to provide further evidence for its validity.

Compound XXXII was converted into the benzoate (XXXV), 3,5-dinitrobenzoate (XXXVI), and p-toluenesulfonate (XXXVII) by standard methods. After chromatographic purification, the colorless, syrupy, 1,2-O-isopropylidene-3-O-benzoyl-5-deoxy-β-L-arabinofuranose (XXXV) showed satisfactory infrared and n.m.r. (given as Figure 6) spectra. In particular, a simultaneous consideration of the n.m.r. spectra of XXXII and XXXV furnishes conclusive evidence for the structures of these compounds.

The presence of a single benzoyl group is shown by the disappearance of the broad hydroxyl hydrogen absorption at 6.34 τ in the spectrum of XXXII and the fact that the integration of the spectrum of XXXV is consistent with the structure of a monobenzoate. None of the absorptions in the spectrum of XXXV were observed to change position markedly with changes in concentration.

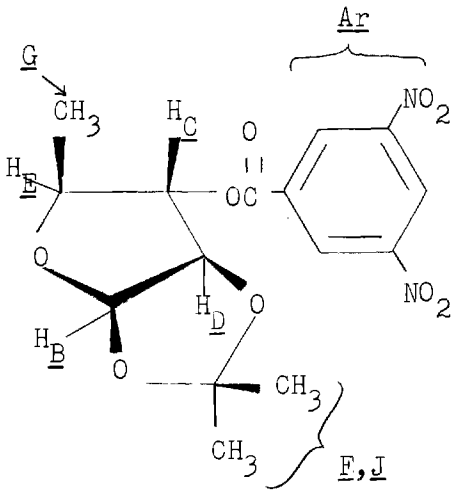


XXXVI

H	τ	J, cps
Ar	1.9-2.7	(not analyzed)
B	4.02	BD = 4.2
C	4.81	CD = 0
D	5.28	CE = 1.8
E	5.67	EG = 7.0
F	8.43	
G	8.49	
J	8.68	

The benzoylation of the hydroxyl group of XXXII produced the characteristic downfield shift (5.96 to 4.81 τ) in the absorption position of the hydrogen attached to the same carbon that bears the hydroxyl group (109,110). This shift resulted in the complete separation of the absorptions of the ring hydrogens. For this reason a complete observation of all of the couplings between these hydrogens is possible. Since the absorption at 5.67 τ is a quartet ($\underline{J}$ = 7.0) of doublets ($\underline{J}$ = 1.8), it must be assigned to the C_4 hydrogen, which would be expected to be coupled to both the terminal methyl group (which absorbs as a doublet, $\underline{J}$ = 7.0) and to the hydrogen that also shows a coupling constant of 1.8 cps. Because the hydrogen that was shifted downfield absorbs as a doublet with $\underline{J}$ = 1.8 cps, it follows that the hydroxyl group of XXXII must be attached at C_3. The lack of significant changes in the rest of the spectra of XXXII and XXXV indicates that no other significant structural change has occurred during benzoylation.

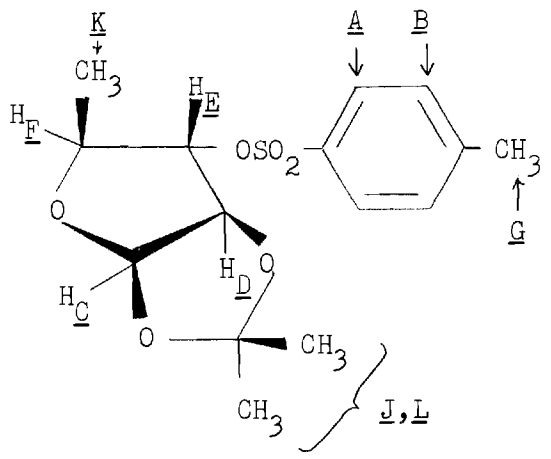
The crystalline 1,2-O-isopropylidene-3-O-(3,5-dinitrobenzoyl)-5-deoxy-β-L-arabinofuranose (XXXVI) gave a satisfactory elemental analysis and showed structurally consistent infrared and n.m.r. (given as Figure 7) spectra. The n.m.r. spectrum of XXXVI is similar in most respects to that of XXXV. The observation of similar multiplicities and positions for the absorptions further substantiates all of the conclusions made above concerning the structure of these compounds. That the downfield shift of the absorption due to the C_3 hydrogen is greater for the 3,5-dinitrobenzoylation of XXXII (5.96 to 4.75 τ) than for the benzoylation (5.96 to 4.81 τ) is consistent with the relative electronegativities of the two different aromatic groups.



H	τ	J, cps
Ar	0.72-0.88	(not analyzed)
B	4.03	BD = 4.2
C	4.75	CD = 0
D	5.15	CE = 1.8
E	5.59	EG = 7.0
F	8.41	
G	8.47	
J	8.62	

XXXVI

The crystalline 1,2-O-isopropylidene-3-O-(p-toluenesulfonyl)-5-deoxy-β-L-arabinofuranose (XXXVII) gave a satisfactory elemental analysis and showed structurally consistent infrared and n.m.r. (given as Figure 8) spectra. p-Toluenesulfonation of XXXII did not produce as large a shift in the absorption of the C_3 hydrogen (5.96 to 5.41 τ) as did benzoylation. The general similarity between the spectra of XXXV and XXXVII



H	τ	J, cps
A	2.18	AB = 8
B	2.63	CD = 4.1
C	4.18	DE = 0
D	5.39	EF = 2.8
E	5.41	FK = 6.9
F	5.83	
G	7.57	
J	8.51	
K	8.70	
L	8.73	

XXXVII

substantiates all of the conclusions concerning the structure of XXXII.

Because of the previously observed utility of the chromium trioxide-pyridine complex in the oxidation of methyl 2,3-O-isopropylidene-α-L-rhamnopyranoside (XVIII), nine attempts to oxidize XXXII with this reagent were made. The results of these oxidations are summarized in Table 3.* The yields given for the product do not reflect the composition of this material. In general, the infrared spectra of the products were poorly defined and usually showed several absorptions in the 5.6-6 μ region. The poor recoveries probably resulted from further oxidation of the product and/or the general decomposition of the reactant under the reaction conditions. It was concluded that the chromium trioxide-pyridine complex is not suited for the oxidation of furanose cyclic secondary hydroxyl groups.

The oxidation of XXXII with chromium trioxide in acetone was next attempted. The use of this reagent in the oxidation of several protected pyranosides has been reported (67). The products obtained from the three reactions performed showed infrared spectra that were similar (poorly defined) to those of the products of the chromium trioxide-pyridine oxidations. Since the yields were poor and the product did not appear to be homogeneous, this method was abandoned.

The Oppenauer oxidation of cyclic secondary steroid alcohols has been shown to give good yields of the corresponding ketones (111). The mild conditions required gave promise to the applications of this method to the oxidation of XXXII. When acetone and aluminum tert-butoxide were

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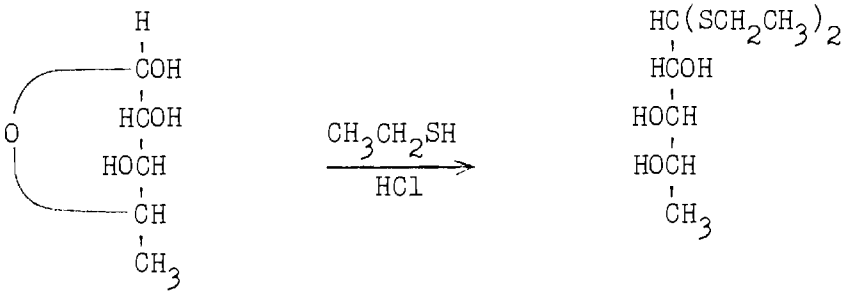
* Page 47, this thesis.

used, there was obtained a 90 per cent recovery of the starting material. The observed lack of oxidation was probably due to the low oxidation potential of acetone (112). Another attempt was made using p-benzoquinone (which has a much higher oxidation potential). The quinone was very difficult to remove from the product. Although starting material was recovered in poor yield, the infrared spectrum of the crude product did not indicate the presence of a carbonyl component other than quinone. Since no evidence was obtained that indicated any oxidation was obtained under Oppenauer conditions, this method was abandoned.

Catalytic oxidation (using platinum and oxygen) of carbohydrate secondary alcohols is well known (113). An attempt to oxidize XXXII by a standard procedure (114) resulted in the uptake of 82 per cent of the required amount of oxygen and the recovery of 60 per cent of the starting material. These observations are not consistent for the production of the desired ketone. The large oxygen consumption must be due to the further oxidation of the assumed product. Since the infrared spectrum of the product showed no evidence of a carbonyl component, the method was not applied further.

Because the oxidation of XXXII was not proceeding satisfactorily under a variety of conditions, several attempts were made to obtain another derivative of 5-deoxy-L-arabinose that had a single free hydroxyl group at C_3. For this purpose the known 5-deoxy-L-arabinose diethyl dithioacetal (XXXVIII) was prepared essentially according to the method of Levene and Compton (55). The observed properties of this material are in agreement with those reported.

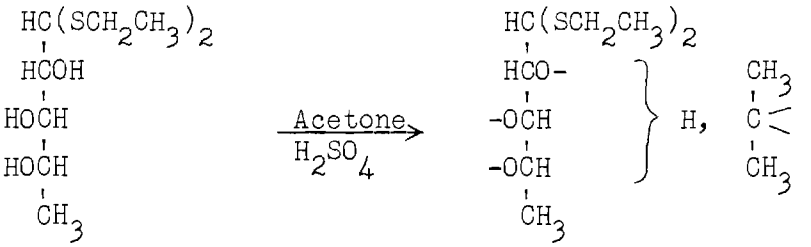
The formation of acetal derivatives of the hexitols has been the



XXXIII XXXVIII

subject of considerable investigation (115). As a result of this work a set of empirical rules has been formulated that predict the position of attachment of different types of acetal protecting groups for the hexitols (115). If these rules are applicable then XXXVIII would be expected to yield a 2,3-O-isopropylidene derivative and a 2,4-O-methylene derivative.

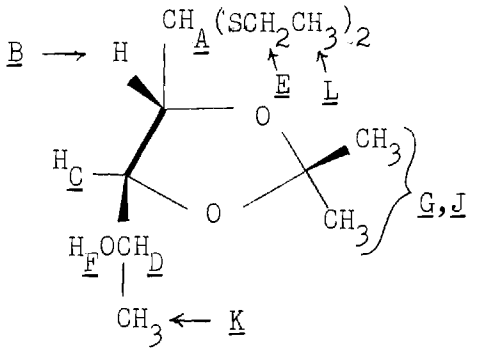
Acetonation of XXXVIII gave a 66 per cent yield, after chromatography, of a yellow syrup that showed infrared and n.m.r. (given as Figure 11) spectra that were satisfactory for a mono-isopropylidene derivative (XXXIX). The compound was chromatographically homogeneous and was converted into a crystalline 3,5-dinitrobenzoyl derivative (XL).



XXXVIII XXXIX

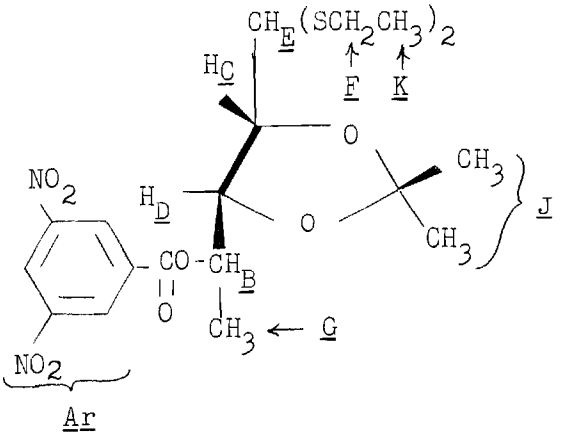
Compound XL gave a satisfactory elemental analysis (for a mono-3,5-dinitrobenzoyl derivative) and showed consistent infrared and n.m.r.

spectra. The simultaneous consideration of the n.m.r. spectra of compounds XXXIX and XL indicates that the expected 2,3 orientation of the isopropylidene group has been obtained.



XXXIX

H	τ	J, cps
A-D	5.64-6.23	DK = 6.1
E	7.27	EL = 7.5
F	7.69	
G	8.54	
J	8.62	
K	8.72	
L	8.74	



XL

H	τ	J, cps
Ar	0.94	BD = 6.0
B	4.78	BG = 6.5
C	5.73	CD = 5.8
D	5.93	CE = 5.5
E	6.19	FK = 7
F	7.33, 7.37*	
G	8.52	
J	8.61	
K	8.78	

The n.m.r. spectrum of XXXIX shows a number of overlapping absorptions in the 5.64-6.23 τ region, none of which can be assigned with

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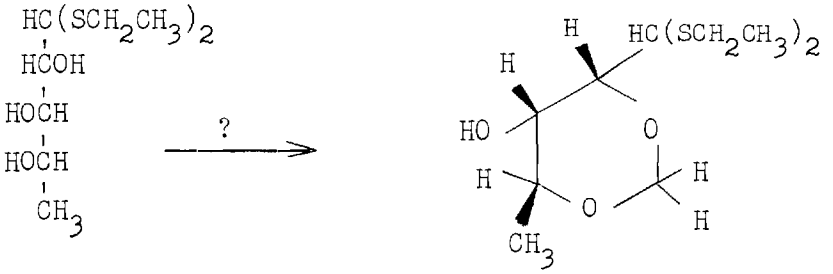
* The non-equivalence of the methylene group protons is caused by the pseudoasymmetry of C_1.

certainty. The n.m.r spectrum of XL is well resolved and as a result, the unambiguous assignment of all of the absorptions is possible. Acylation of the free hydroxyl group of XXXIX caused a shift in the absorption position of the C_4 hydrogen. This is apparent, since this hydrogen is the only single hydrogen present that could absorb as a quintet.

The fact that XXXIX gave a positive iodoform test is additional confirmation of the assigned structure. Based on these data, compounds XXXIX and XL are assigned the structure shown above and are correctly named 2,3-O-isopropylidene-5-deoxy-L-arabinose diethyl dithioacetal and 2,3-O-isopropylidene-4-O-(3,5-dinitrobenzoyl)-5-deoxy-L-arabinose diethyl dithioacetal, respectively.

Since the acetonation of XXXVIII proceeded as expected, several attempts were made to obtain the predicted 2,4-O-methylene derivative. The normal methylenation of hexitols involves the use of aqueous acid and paraformaldehyde. The n.m.r. spectrum of the product formed in poor yield



XXXVIII

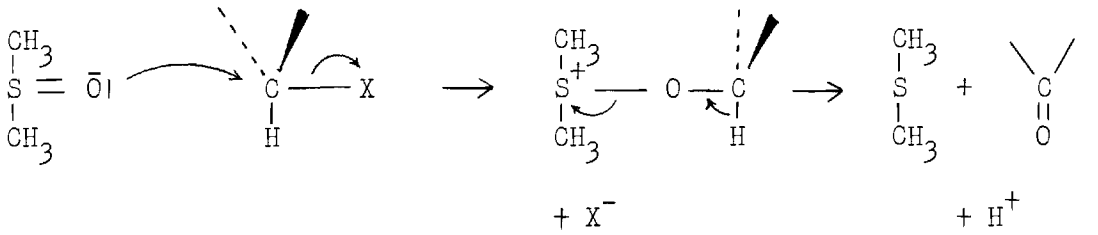
from XXXVIII under these conditions was not satisfactory for a methylene derivative. Integration of this spectrum indicated that the product was a complicated mixture. Further attempts to methylenate XXXVIII using either aqueous dioxane and formaldehyde or anhydrous dioxane and paraformaldehyde both in the presence of acid, resulted in the complete

removal of the thioethyl groups, as indicated by the n.m.r. spectra of the product (which is probably a mixture of methylene derivatives of 5-deoxy-L-arabinose). Because a methylene derivative of XXXVIII is the only acetal derivative that would be expected to be attached at C_2 and C_4, this approach was abandoned.

The utility of dimethyl sulfoxide (DMSO) as an oxidizing agent has been developed considerably in recent years (116-121). The specificity of the oxidizing action of the reagent, as well as other features, prompted the application of some of these methods to the problem of the oxidation of XXXII.

Kornblum and co-workers have described the oxidation of primary alcohol p-toluenesulfonates to aldehydes by the action of DMSO and sodium bicarbonate at 100-150° (119). While the oxidation of secondary alcohol p-toluenesulfonates is less well known (116), the results obtained for the oxidation of a few secondary halides with DMSO indicate that lower yields are to be expected (117,118). The proposed mechanism of these DMSO oxidations involves an S_N2 displacement of the halide or tosylate group followed by the concerted loss of a proton and release of dimethyl sulfide to give the carbonyl compound (117,118). The observation of dimethyl sulfide as a major product, the observed variation in yield with different halides (I Cl), and the selectivity (other oxidation-sensitive groups are not affected) of the reagent all support this mechanism.

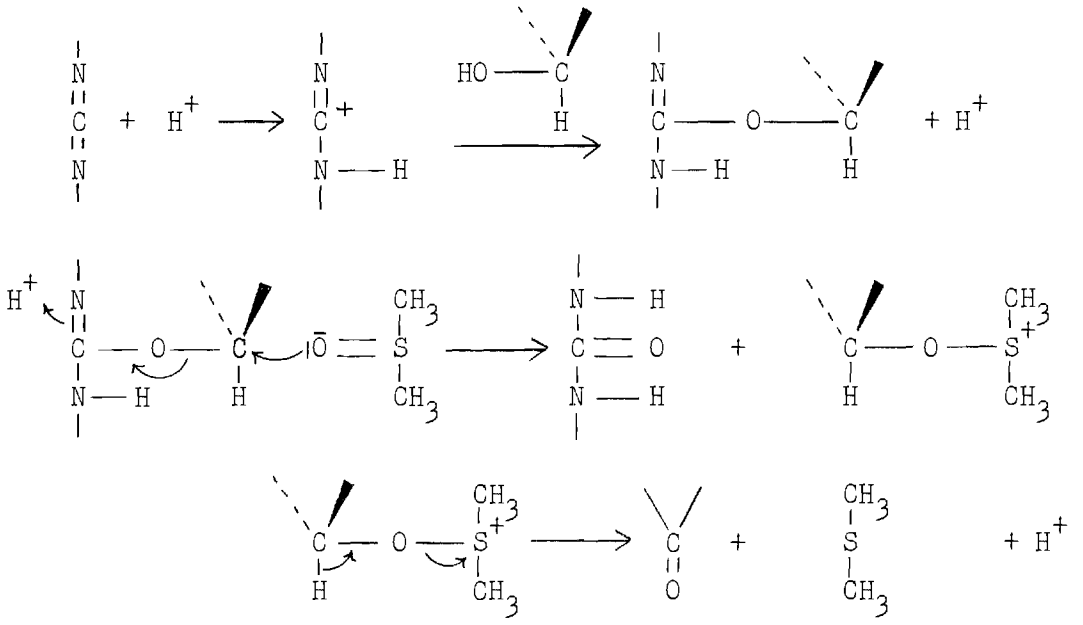
While the temperature required for the reaction (100-150°) might cause some general decomposition of carbohydrate materials, investigation of the oxidation of XXXVII seemed desirable. l-Menthyl p-toluenesulfonate was chosen as a model compound for this reaction and was prepared



as described previously (57). The action of a hot solution of sodium bicarbonate in DMSO on l-menthyl p-toluenesulfonate gave a small amount of l-menthone (isolated as the 2,4-dinitrophenylhydrazone). When more vigorous conditions were applied to the oxidation of XXXVII, an almost quantitative recovery of the starting material was obtained. Since more vigorous conditions would probably destroy the product if oxidation did occur, this method was abandoned.

Pfitzner and Moffatt have observed the selective oxidation of primary and secondary alcohols with an anhydrous solution of N,N'-dicyclohexylcarbodiimide (DCC), pyridinium phosphate, and DMSO (120). The reaction was shown to produce dimethyl sulfide and N,N'-dicyclohexylurea (DCU), to require acid catalysis, and to be dependent on the steric environment of the alcohol function.

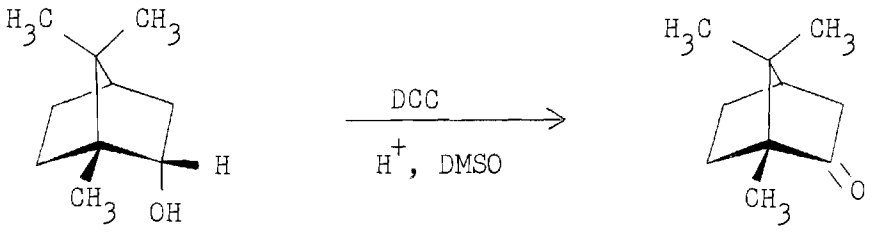
On the basis of these data and the previous work regarding similar DMSO oxidations, the mechanistic sequence shown below is herein proposed for the oxidation of primary and secondary alcohols with DMSO in the presence of DCC and pyridinium phosphate. The first step would be the addition of the alcohol oxygen to a protonated DCC molecule (thus the requirement for acid catalysis) to give an intermediate isourea. Displacement of the urea fragment would be expected to be much more easily accomplished than that of a halide or p-toluenesulfonate residue since the



DCU would be expected to be a better leaving group. It is important in this regard to note that the DMSO oxidation of alkyl chlorides is much less facile than that of the corresponding iodides (118), as would be expected, since iodide is more easily displaced by S_N2 attack than chloride (122). Precedents for the formation of the DCC-alcohol intermediate have been reported (123). The final concerted loss of a proton and release of dimethyl sulfide is identical to that portion of the mechanism proposed for the DMSO oxidation of alkyl halides.

The specificity of the reaction and the mildness of the conditions make this method the most promising for the oxidation of XXXII. Although acid catalysis is required, the absence of water in the reaction medium should prevent the removal of the isopropylidene group of both the reactant and product.

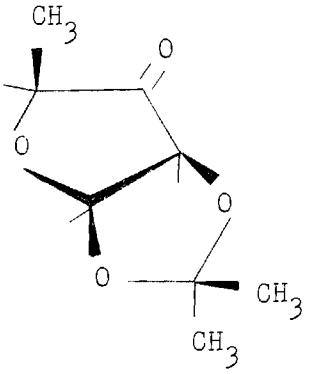
Because of the possible effect of the steric hindrance to S_N2 attack on compound XXXII according to the proposed mechanism, borneol was chosen as a model compound for this oxidation.



Borneol Camphor

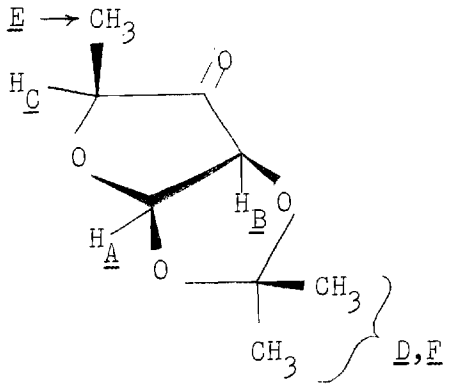
Under the oxidation conditions described, borneol gave a 52 per cent yield of camphor (isolated as the 2,4-dinitrophenylhydrazone). The similarity of the steric environments of the alcohol groups of borneol and XXXII makes this oxidation a significant precedent.

The oxidation of XXXII was next attempted using conditions similar to those for the oxidation of borneol. The first attempted isolation of the product was unsuccessful. After filtration of the precipitated DCU, the benzene was evaporated and the DMSO was removed by lyopholization. The infrared spectrum of the small amount of solid orange residue indicated that primarily DCU was present. Since neither the product nor reactant could be located, one or both must have sublimed or distilled during the low pressure lyopholization. Another reaction was performed and the sublimate was diluted with water (which had to be avoided before the removal of the pyridinium phosphate). Continuous extraction of the solution with cyclohexane for several days gave good yields (51-72%) of the desired 1,2-O-isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose (XLI). The product was a colorless mobile liquid that showed satisfactory infrared (Figure 9) and n.m.r. (Figure 10) spectra. A sample of XLI that had co-distilled with cyclohexane was chromatographically

XXXII $\xrightarrow[H^+,\ DMSO]{DCC}$ 

XLI

homogeneous (TLC, two systems). Compound XLI was not stable at room temperature whether neat or in solution (as evidenced by changes in the infrared and n.m.r. spectra). In particular, the compound could not be chromatographed over silicic acid without decomposition.

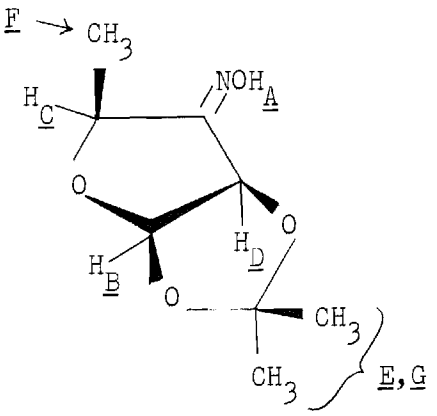


XLI

H	τ	J, cps
A	4.02	AB = 4.4
B	5.53	BC = 0.9
C	5.77	CE = 7.2
D	8.50	
E	8.55	
F	8.59	

Compound XLI was further characterized by means of a crystalline oxime derivative. 1,2-O-Isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose oxime (XLII) gave satisfactory elemental analyses and showed satisfactory infrared and n.m.r. spectra.

The structures of XXXII and all subsequent transformation products are further confirmed by the n.m.r. spectra of XLI and XLII.



H	τ	J, cps
A	1.00	BD = 4.0
B	4.13	CF = 6.7
C	5.02	
D	5.11	
E	8.41	
F	8.43	
G	8.62	

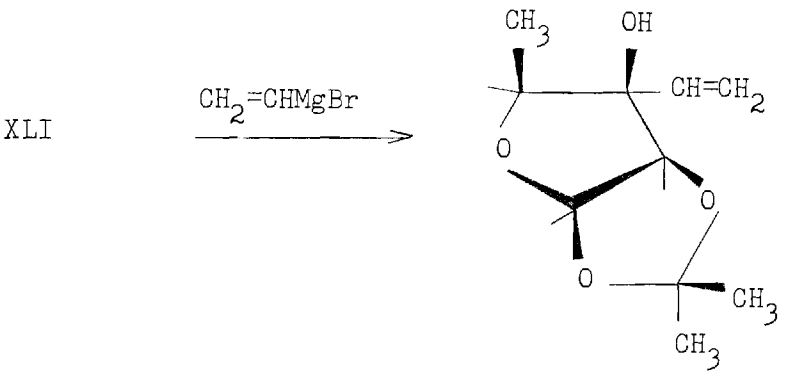
XLII

The major significance of these two spectra is that the presence of all of the absorptions except those assigned to the C_3 hydrogen and the hydroxyl hydrogen of XXXII conclusively confirms all of the previous n.m.r. assignments. This provides strong evidence that as long as the n.m.r. absorptions of the hydrogens present at C_1, C_2, C_4, and C_5 in these compounds are not appreciably or significantly altered in multiplicity or position, the stereochemistry at these carbon atoms of the subsequent transformation products must be the same as that of XXXII.

Overend has noted that the oxidation of secondary furanose hydroxyl groups is difficult to achieve (72). Recently, Beynon, Collins, and Overend reported that this type of oxidation can be achieved in good yield (80%) using ruthenium tetroxide (124).

The next reaction in the proposed synthesis of streptose is the addition of vinylmagnesium bromide to XLI. The fact that methyl 2,3-O-

isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose (XIX) gave only one of the possible isomeric Grignard addition products serves as an impor-

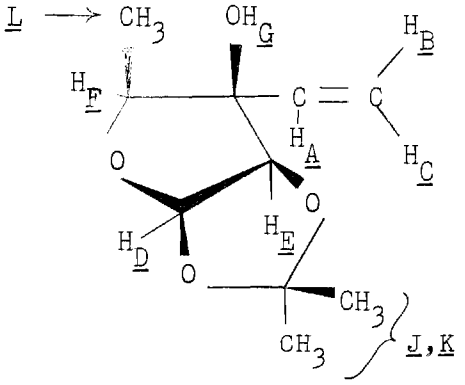


XLIII

tant precedent for the present reaction. Since the vinyl Grignard addition to XIX gave only the talo configuration (compound XXIII), it would be expected that a similar stereospecific reaction would occur between vinylmagnesium bromide and XLI to give 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (XLIII). An examination of molecular models indicates that one side of the carbonyl group of XLI is more sterically hindered than the corresponding side of XIX. This is a direct result of the fact that the furanose ring of XLI is smaller than the pyranose ring of XIX. Because the Grignard addition to XIX proceeded according to Cram's steric model prediction, rather than the cyclic intermediate prediction (as discussed previously), the Grignard addition to XLI, which has greater steric requirements than XIX, was expected to yield only the lyxo isomer.

When XLI was reacted with a large excess of vinylmagnesium bromide

in THF, there was obtained a 104 per cent yield of crude crystalline product (the higher-than-theoretical yield is probably due to vinyl polymer formation). The product showed only one volatile component when analyzed by GLC. After sublimation, the product constituted a 70 per cent yield and was chromatographically homogeneous. The compound gave an elemental analysis and showed infrared and n.m.r. (Figure 13) spectra that were all satisfactory for 1,2-O-isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose (XLIII). The n.m.r. spectrum in particular indicated the lyxo configuration of XLIII.



XLIII

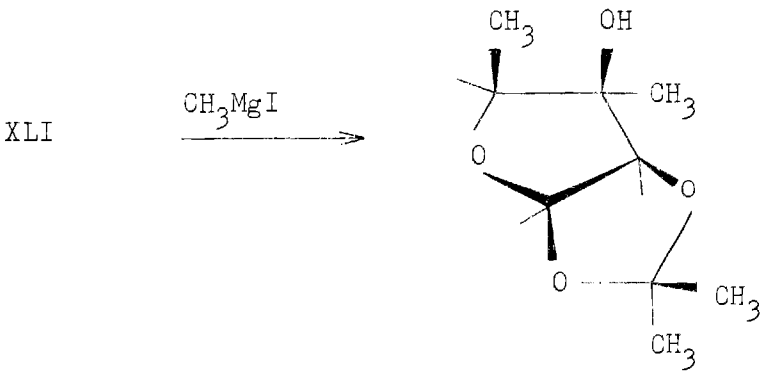
H	τ	J, cps
A	4.09	AB = 17.4
B	4.58	AC = 9.9
C	4.83	BC = - 2.8
D	4.29	DE = 4.5
E	5.60	FL = 6.7
F	6.13	
G	6.89	
J	8.38	
K	8.62	
L	8.73	

The initial sublimation residues from several preparations of XLIII were combined and carefully chromatographed over silicic acid. The third through fifth column volumes of eluent contained an additional amount of crystalline XLIII. This observation is further evidence for the lyxo configuration since in this configuration the hydroxyl group is more sterically hindered and thus less able to interact with the polar adsorbant (84) than would be expected for the arabino configuration. Compound XXXII,

which has the arabino configuration, is not eluted under similar conditions until after the seventh column volume of eluent.

Examination of later chromatography fractions showed the presence of very small amounts of another solid material. After recrystallization, the physical properties of this material were identical to those of N,N'-dicyclohexylurea. As mentioned previously, compound XLI was usually contaminated with small amounts of this material. The syrupy materials from later chromatography fractions exhibited poorly defined n.m.r. spectra and are probably vinyl polymers.

Because of the facility of the vinyl Grignard reaction, the methyl Grignard reaction was performed and gave a 30 per cent yield (after chro-

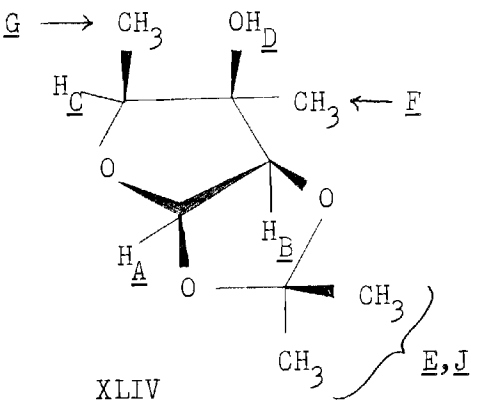


XLIV

matography) of white crystalline 1,2-O-isopropylidene-3-C-methyl-5-deoxy-β-L-lyxofuranose (XLIV). The non-crystalline chromatography fractions were not exhaustively examined for the arabino isomer of XLIV. GLC analysis of the crude product (before chromatography) indicated the presence of another volatile component. Because the infrared spectrum of this

material showed carbonyl absorption (5.64 μ) at the same position as that of the starting ketone (XLI), the other volatile component (with a shorter retention time) was probably unreacted XLI.

Purified XLIV was chromatographically homogeneous (GLC), gave a satisfactory elemental analysis, and showed consistent infrared and n.m.r. spectra. Both the n.m.r. spectrum and silicic acid chromatography (the

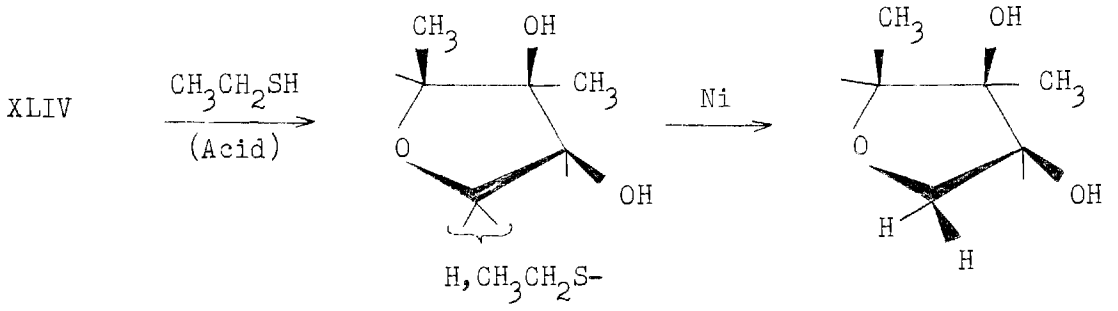


XLIV

H	τ	J, cps
A	4.31	AB = 4.3
B	5.79	CG = 6.7
C	6.20	
D	7.03	
E	8.40	
F	8.64	
G	8.69	
J	8.71	

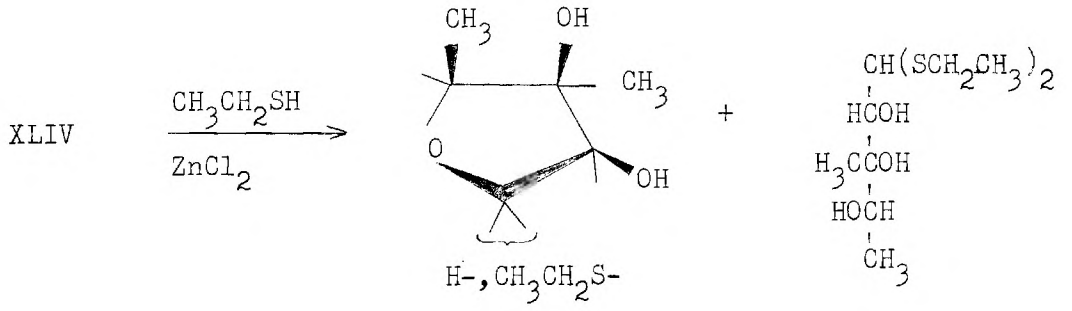
compound was eluted mainly in the fourth through sixth column volumes of eluent) provide evidence for the lyxo configuration of the product.

Compound XLIV was prepared for an attempted synthesis of L-dideoxydihydrostreptose (Compound X, (19,62)). The reaction sequence shown below was proposed.



Displacement of anomeric acetals and anomeric acetyl groups by ethanethiol in the presence of some acid, to give a mixture of thioglycosides and thioacetals is well known (125). Although a mixture of products is usually obtained, longer reaction times and higher temperatures favor the formation of thioglycosides (125,126).

Mercaptolysis of XLIV was studied extensively with the application of the procedure of Wolfrom and Thompson (127). Analysis of the n.m.r. spectra of the crude reaction products was used to estimate their composition. In all instances, the absorption due to the isopropylidene methyl

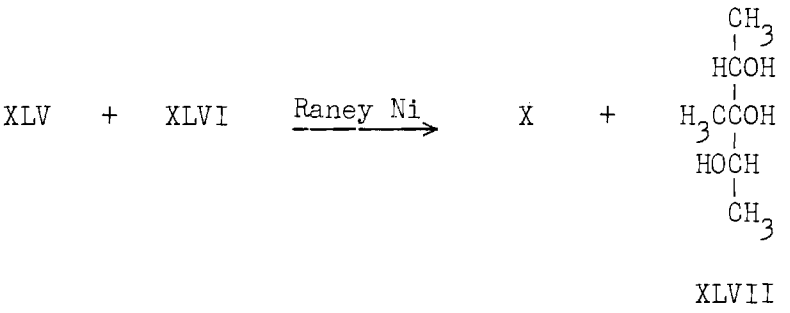


XLV XLVI

groups of XLIV had disappeared after a reaction time of at least one day. Since the mercaptolysis products would be expected to show complicated absorption in the 5-7 τ region, the ratio of the integration of the methyl groups absorption (8.6-9.0 τ) to that of the methylene absorption (7.0-7.6 τ) was used as an indication of the product composition. The theoretical value for this ratio is 4.5 for XLV and 3.0 for XLVI. It was observed that higher reaction temperatures and longer times gave products

with higher ratios (one day at 0° gave a product with a ratio of 2.8 while six days at 25° gave a product with a ratio of 4.3).

The crude mercaptolysis products were desulfurized directly since separation of the products of this reaction seemed more likely. Compound



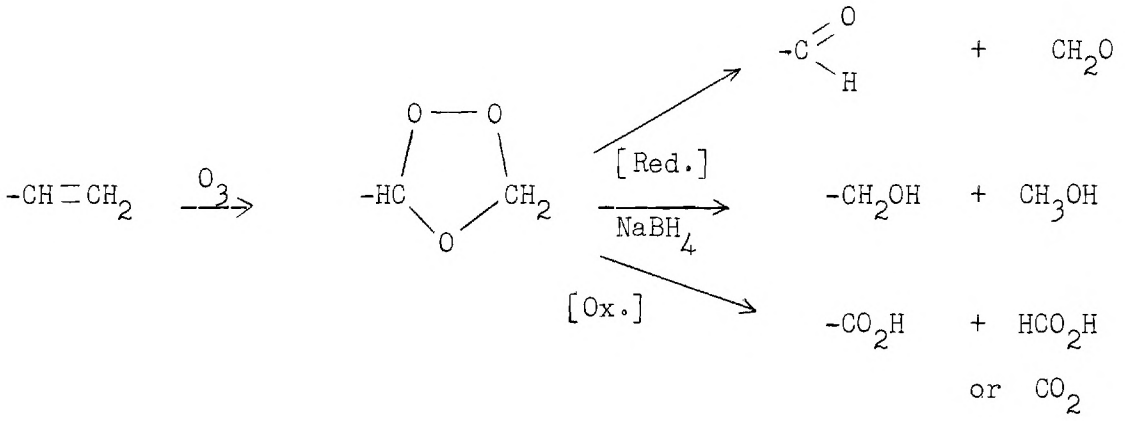
XLVII

X is known to be soluble in chloroform (19), whereas XLVII, because of the presence of three hydroxyl groups, would not be expected to be very chloroform-soluble.

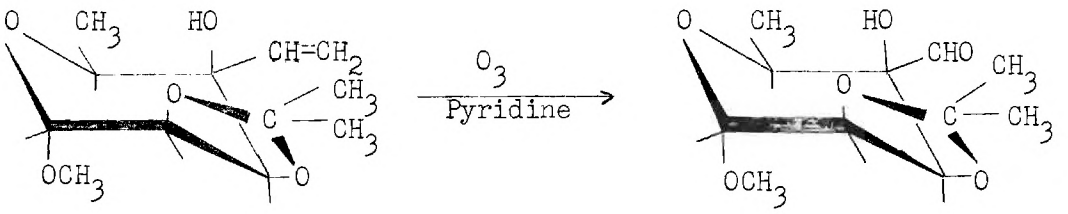
The compositions of the crude desulfurization products were investigated by both n.m.r. and GLC. It was observed that mercaptolysis products that showed low CH_3/CH_2 n.m.r. integration ratios gave very small amounts of chloroform-soluble material after desulfurization. The n.m.r. spectra of these desulfurization products indicated that they were complex mixtures. The two mercaptolysis products that had the highest CH_3/CH_2 integration ratios (4.34 and 4.21) gave desulfurization products that were complicated mixtures. GLC analysis of the first desulfurization product showed six peaks and a similar analysis of the second product showed five peaks. While both products showed a peak at about the same retention time as a sample of authentic L-dideoxydihydrostreptose, the fact that the relative amounts of that particular component were small (14% and 2%) and the overall complexity of the products discouraged purification attempts.

No further attempt was made to synthesize X.

The next reaction in the proposed synthesis of streptose involved the ozonolysis of XLIII. It was anticipated that the ozonide could probably be decomposed under different conditions and give the corresponding 3-C-formyl, 3-C-carboxyl, or 3-C-hydroxymethyl compounds.

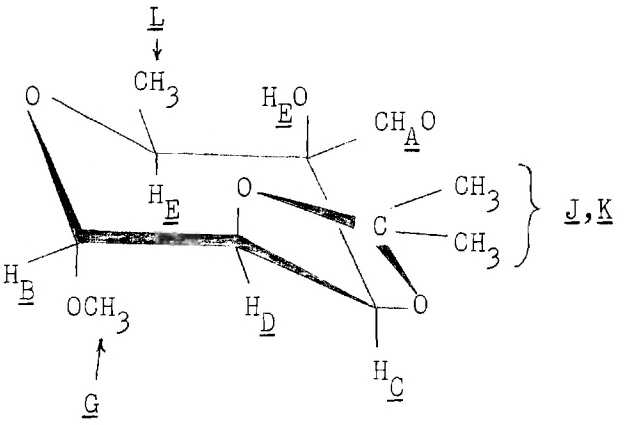


A novel method that gave aldehydes directly during the ozonolysis was first utilized (128). The presence of pyridine during the ozonolysis causes the direct decomposition of the ozonide to give two aldehydes and pyridine N-oxide (128). As a model for the reaction, the ozonolysis of XXIII was performed and gave a 58 per cent yield of a syrup that exhibited



XXIII XLVIII

infrared and n.m.r. spectra that were consistent with the structure of the expected product. An attempt to purify the product by silicic acid chro-

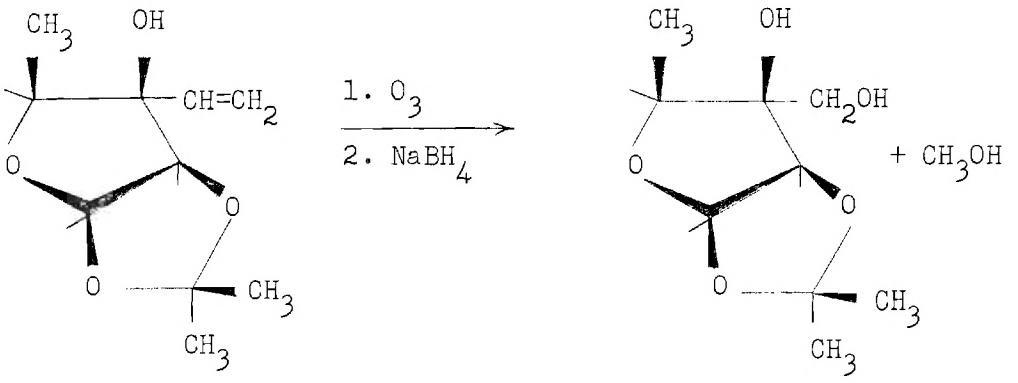


XLVIII

H	τ	J, cps
A	0.44	BD = 0
B	5.20	CD = 7
C	5.63	EL = 7
D	6.02	
E	6.29	
F	6.67	
G	6.70	
J	8.51	
K	8.74	
L	8.93	

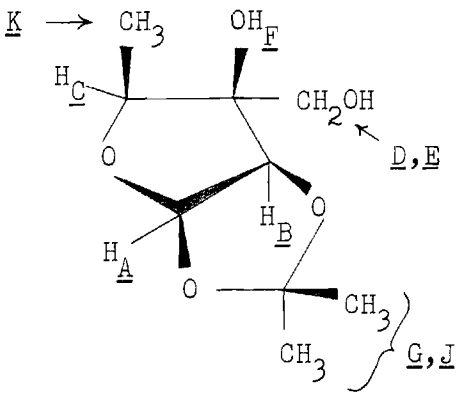
matography resulted in changes in the n.m.r. and infrared spectra of the material eluted, which indicated that considerable decomposition had occurred.

The application of this particular ozonolysis procedure to compound XLIII resulted in the production of a complex mixture of materials, as evidenced by the infrared and n.m.r. spectra of the product.



XLIII XLIX

Ozonolysis of XLIII was next attempted using the method of Witkop and Patrick (129,130). Reductive decomposition of the ozonide of XLIII was accomplished with sodium borohydride. The product was a soapy solid that slowly crystallized when allowed to stand at room temperature. Sublimation of this material gave a 71 per cent yield of white crystalline 1,2-O-isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose (XLIX). The compound gave an acceptable elemental analysis and showed consistent infrared and n.m.r. (Figure 14) spectra.

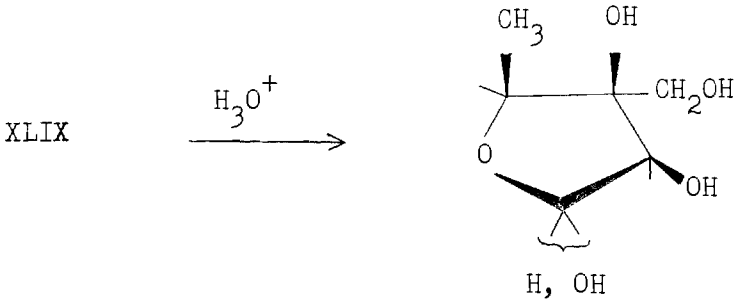


XLIX

H	τ	J, cps
A	4.26	AB = 4.5
B	5.46	CK = 7.1
C	6.13	DE = -12.4
D	6.40	
E	6.56	
F	6.92	
G	8.38	
J	8.61	
K	8.67	

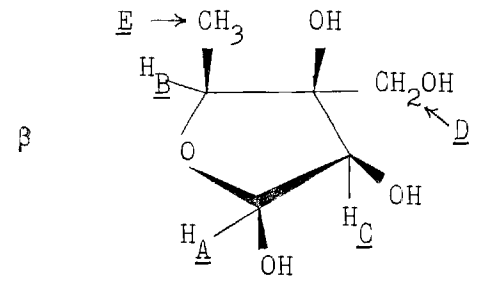
A preliminary paper chromatographic investigation of the removal of the isopropylidene group of XLIX indicated that hydrolysis was complete after two days at room temperature in the presence of aqueous Dowex 50W-X8 (H^+). A large scale preparation of L-dihydrostreptose (L) gave, after carbon-celite chromatography, a 63 per cent yield of a colorless, reducing syrup. Paper chromatography of this syrup showed only one, well-defined spot in both EAW (R_F 0.49, R_G 2.88) and BEW (R_F 0.52, R_G 1.68). The material showed satisfactory infrared (Figure 15) and n.m.r. (Figure

16) spectra.

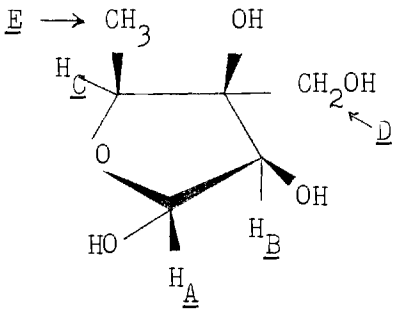


L

The n.m.r. spectrum of L showed absorptions due to two anomeric C_4 furanose isomers. That the $-CH_2-$ group absorbs at about the same position as the analogous group of XLIX indicates the C_4 furanose attachment rather than attachment to the branch hydroxymethyl group. Integration of the methyl group absorptions indicated that the distribution of the



β



α

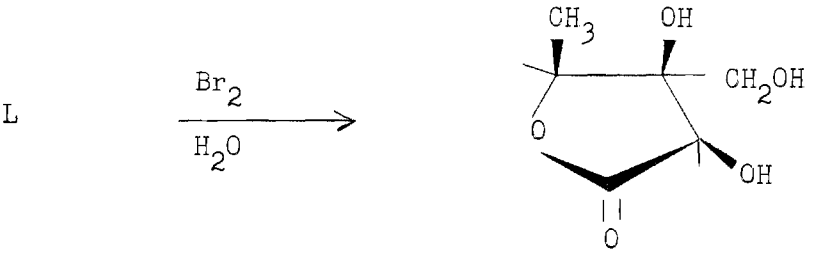
L

H	τ	J, cps
	-β-	
A	4.72	AC = 3.8
B	5.65	BE = 6.6
C	5.85	
D	6.38	
E	8.76	
	-α-	
A	4.76	AB = 5.1
B	5.82	CE = 6.6
C	5.91	
D	6.38	
E	8.71	

two isomers was 74:26. The anomer present in 74 per cent amount is assigned the β configuration on the basis of the magnitude of the observed C_1-H, C_2-H coupling constant. Since furanose rings would be expected to assume the most stable of 10 possible puckered conformations, and since vicinal coupling constants are known to depend on the relative orientation of the two hydrogens, the assignment is tentative.

Application of Brewster's methods for the empirical calculation of optical activity (131) gives additional evidence for the above assignments. Assuming that the average conformation of the furanose ring is planar, the calculated molecular rotation values are -149° for the α anomer and -22° for the β anomer. Since the observed equilibrium value ($[M]_D$ = -39°) corresponds to a mixture containing 74 per cent of one anomer and 26 per cent of the other (as indicated by integration of the n.m.r. spectrum), the predicted value for a mixture containing 74% of the α anomer is -117° and for a mixture containing 74% of the β anomer is -55°. While this result is not conclusive, it does indicate that the β anomer is present in the largest amount.

As a final proof of the identity of the synthetic L-dihydrostreptose (L), the preparation of L-dihydrostreptosonic acid lactone (XV) was



XV

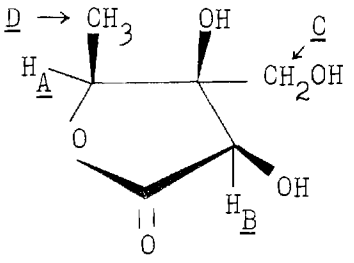
attempted. Bromine water oxidation of L (unchromatographed) gave XV in 60 per cent yield. Compound XV is a reported degradation product of streptomycin and was prepared during the original structure proof of streptose (23). The physical properties of crystalline XV were essentially identical with those reported for the compound derived from streptomycin. A comparison of the observed properties of the synthetic and authentic XV is given below. The infrared and n.m.r. spectra of XV were

Property	Synthetic XV	Authentic XV (23)
m.p.	140.5-142.5°	143-144°
$[\alpha]_D$	-32.7°	-32°
IR, λ_{max}	5.65 μ	5.65 μ

Elemental analysis:

Calc'd.	Found	Found
C, 44.45	C, 44.63	C, 44.02
H, 6.22	H, 6.21	H, 5.87

completely consistent with the structural formula.



XV

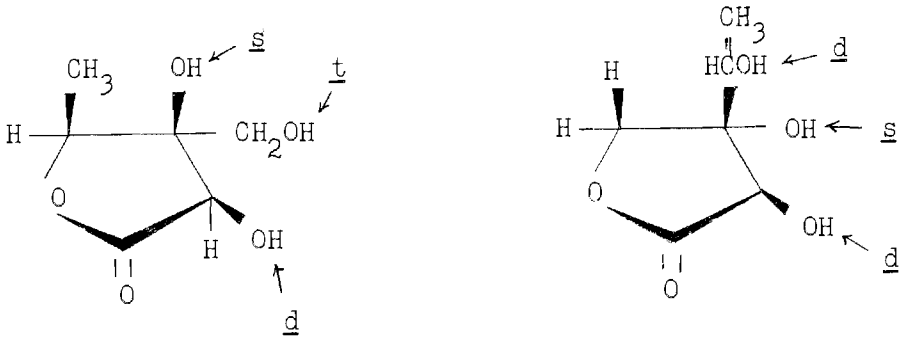
H	τ	J, cps
A	5.37	AD = 6.5
B	5.38	
C	6.38	
D	8.67	

Previous experiments performed using authentic XV indicated that the lactone ring involved the C_4 hydroxyl group and not the primary one (23). Further support for this assignment was obtained from an examination of the n.m.r. spectrum of synthetic XV. As mentioned previously, acylation of a hydroxyl group causes a downfield shift in the position of absorption of the hydrogen(s) attached to the same carbon that bears the hydroxyl group (109,110). Since lactone formation is an intramolecular acylation, a similar shift would be expected. It is observed that the oxidation of L to XV causes the expected change in the position of absorption of the C_4 hydrogen (β-L, 5.65; α-L, 5.91, to 5.37 τ) and no change in that of the CH_2 group (L, 6.38 τ and XV, 6.38 τ).

Recently, Chapman and King have reported that the rate of chemical exchange of the hydroxyl hydrogens of alcohols is sufficiently retarded in dilute DMSO solution so as to permit the observation of spin-spin coupling between the hydroxyl hydrogen and the hydrogen(s) on the same carbon (132-134). Moreover, the positions of absorption of aliphatic hydroxyl hydrogens are shifted downfield into a spectral region (4-5.5 τ) that usually contains very few absorptions. Thus primary alcohols usually absorb as a triplet (coupled to two equivalent hydrogens), secondary alcohols absorb as a doublet (coupled to one hydrogen) and tertiary alcohols absorb as a singlet.

The n.m.r. spectrum of XV in DMSO (5% solution) showed a singlet (1H) at 5.17 τ, a doublet (1H, J = 7.6 cps) at 4.22 τ, and a triplet (1H, J = 4.7 cps) at 4.95 τ. Since the other possible lactone structure (shown at the right, below) would exhibit a singlet and two doublets under these conditions, the observed pattern is further evidence for the assigned

structure.

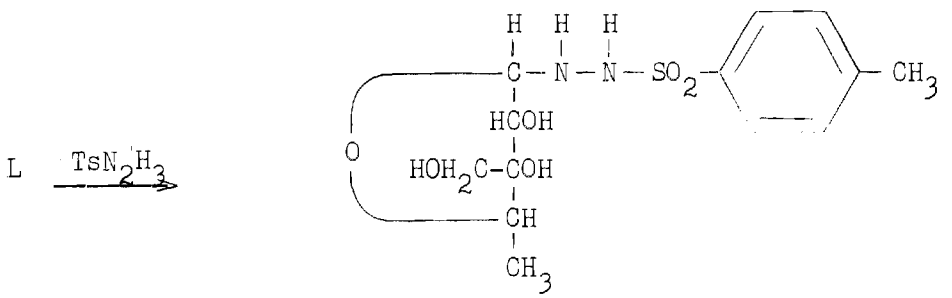


Possible structures for XV

Wang and co-workers have reported that lithium aluminum hydride reduction of naturally derived L-dihydrostreptosonic acid lactone (XV) gave a syrupy mixture of compounds, one of which was claimed to be L-di-

$$\text{XV} \xrightarrow{\text{LiAlH}_4} \text{L} + (?)$$

hydrostreptose (30). No physical properties were reported for the mixture except a single paper chromatography R_F value of 0.32 (attempts to prepare the solvent system reported, 4:1:5, 1-butanol:ethanol:water gave two liquid phases). The reducing mixture gave a crystalline p-toluenesulfonylhydrazone (m.p. 137.5-138°) and a crystalline phenyl osazone (m.p.



160-162°), both of which were claimed to be the corresponding derivatives of L-dihydrostreptose (30). The infrared spectra of the two derivatives were obtained and are presented in the paper. These spectra are of very poor quality; the only absorptions that are present in any prominence are those of nujol.

Because of the availability of synthetic L-dihydrostreptose, several attempts were made to prepare the described p-toluenesulfonylhydrazone derivative. When conditions similar to those described were used, no solid material was produced; furthermore, the syrupy product did not show the solubility properties described. The second attempt employed the more normal conditions (135,136) and gave a 3.6 per cent yield of a crystalline solid. This material could not be recrystallized from THF-methanol as described. After one recrystallization from ether-petroleum ether (b.p. 30-60°), the compound showed a melting point (133-137°) and infrared absorptions similar to those reported. Several other attempts were made to prepare this derivative without success. An attempted preparation of the reported phenyl osazone of L-dihydrostreptose (the conditions used were identical to those given by Wang et al. (30) also failed.

Recently, McGilveray and Stenlake have claimed the isolation of L-dihydrostreptose by acid hydrolysis of methyl N-acetyldihydrostreptobiosaminide, which was obtained from dihydrostreptomycin (29). In this account, L-dihydrostreptose is described as a hygroscopic solid that showed a melting point 135-140° (dec.) and $[\alpha]_D^{21}$ -70° (equilibrium). Paper chromatography of the compound was reported to give a spot at R_F 0.4 in the same solvent system reported by Wang et al. (30). The existence (no mention is made of the preparation) of a sharply melting ("m.p. 173°")

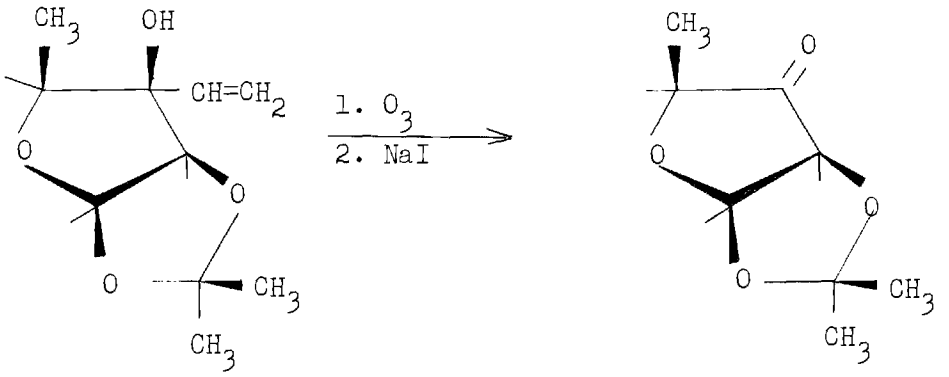
monoacetate of L-dihydrostreptose is mentioned. Since L would be expected to form at least a triacetate under normal acetylation conditions and since sixteen different monoacetates of L are theoretically possible, the nature of this derivative is obscure.

In neither of the above accounts (29,30) was any attempt made to prepare L-dihydrostreptosonic acid lactone from the reported samples of L-dihydrostreptose. In the latter account (29), no attempt was made to prepare the two derivatives of L described by Want et al. (30).

Because of the observation herein of a p-toluenesulfonylhydrazone derivative of L that showed properties somewhat similar to those described by Wang et al., the mixture described by them may have contained some of compound L. The properties of L reported by McGilveray and Stenlake are in complete disagreement with those given herein. It is suggested that their preparation might have been composed mainly of their starting material (methyl N-acetyldihydrostreptobiosaminide, m.p. 140°, $[\alpha]_D$ -125° (29)).

The successful synthesis of L-dihydrostreptose and L-dihydrostreptosonic acid lactone encouraged further attempts to synthesize L-streptose. Because compound XLIII formed an ozonide that was reduced to give XLIX, the investigation of the ozonolysis was continued.

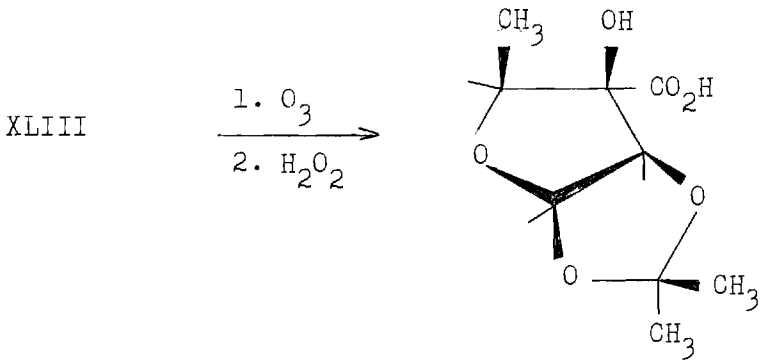
The use of powdered zinc to decompose ozonides reductively is well known (137). When stirred for two days at room temperature with zinc, a solution of the ozonide of XLIII still liberated iodine from aqueous potassium iodide. When this solution was poured into a solution of sodium iodide (precedented mild reduction conditions (137)) there was isolated an 87 per cent yield of XLI (as evidenced by identical infrared and n.m.r.



XLIII XLI

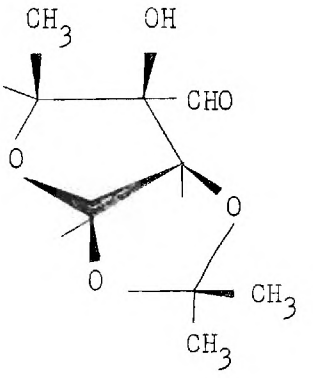
spectra). Such abnormal results are known and presumably involve rearrangement during decomposition of the ozonide (137). A repetition of the reaction, when the zinc treatment was omitted, gave an 86 per cent yield of XLI.

An attempt to decompose the ozonide of XLIII oxidatively with hot 30 per cent hydrogen peroxide, under conditions similar to those described elsewhere (138,139), gave a poor yield of a yellow syrup that showed two



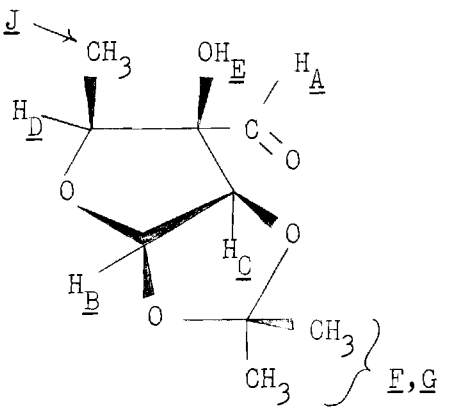
carbonyl absorption bands at 5.75 and 5.85 μ in the infrared region. Since the properties of the product indicated that a complex mixture was present, this method was abandoned.

Catalytic reduction of ozonides with hydrogen and palladium is well known (137). The ozonide of XLIII was treated as previously described (129,140). After the solution of the ozonide in ethyl acetate was added to a slurry of 5 per cent palladium on carbon at 0°, the mixture consumed 0.99 equivalents of hydrogen before reduction stopped. The product (LI) was a colorless, reducing syrup. Integration of the n.m.r. spectrum of this preparation indicated that the component that showed aldehyde proton absorption (0.33 τ) was present in an amount of about 30 per cent. The

XLIII $\xrightarrow[2.\ H_2/Pd]{1.\ O_3}$ 

LI

physical properties (solubility, spectra) of the product changed on standing either neat or in solution at room temperature. The infrared spectrum of freshly prepared LI showed intense, sharp carbonyl absorption at 5.78 μ. This absorption gradually diminished in intensity until after one week it was about one-half of the original value. Freshly prepared



H	τ	J, cps
A	0.25	BC = 4.3
B	4.23	DJ = 6.5
C	5.38	
D	5.93	
E	6.87	
F	8.36	
G	8.56	
J	8.69	

LI

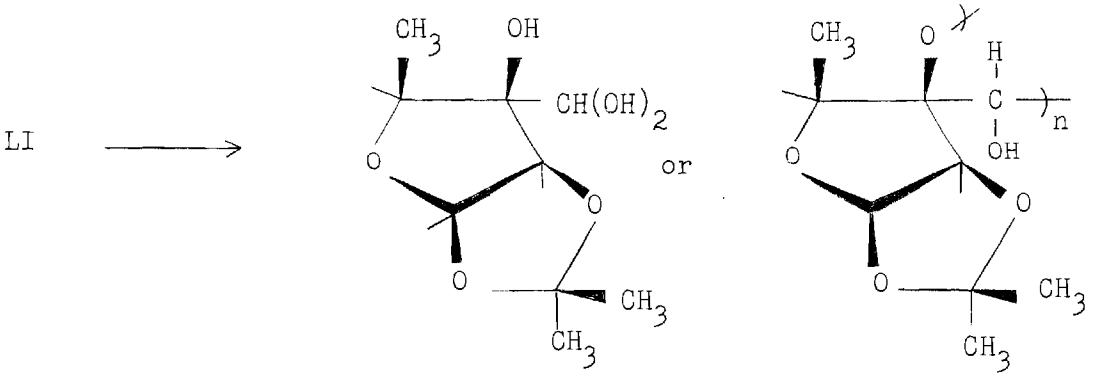
LI was freely soluble in carbon tetrachloride, but material gradually separated from the solution as a very viscous syrup after one day. This syrup was insoluble in hot water. The product could be partially sublimed (which would be expected since XLIX sublimes readily); however, the solid sublimate could be only partially resublimed. An n.m.r. spectrum obtained on a freshly sublimed portion was somewhat satisfactory for 1,2-O-isopropylidene-3-C-formyl-5-deoxy-β-L-lyxofuranose (LI). Integration of this spectrum was not completely satisfactory for LI, but indicated that LI was present to an extent of about 60 per cent.

Some aldehydes such as chloral, form stable crystalline hydrates and others such as acetaldehyde and formaldehyde, form trimers and polymers. The above properties of material obtained from catalytic reduction of the ozonide of XLIII indicate that either polymerization or hydrate formation was occurring. In order to verify that the product had a potential aldehyde group, a sample (that had stood at room temperature for one week) was reduced with sodium borohydride and gave a 55 per cent yield of 1,2-O-isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose (XLIX).

$$\text{LI} \xrightarrow{NaBH_4} \text{XLIX}$$

Compound XLIX, prepared in this manner, showed melting point (the mixture melting point was not depressed), specific rotation, and infrared spectra that were identical to those of XLIX obtained by direct sodium borohydride reduction of the ozonide of XLIII. The formation of this compound shows that no gross structural change had occurred during the preparation of LI.

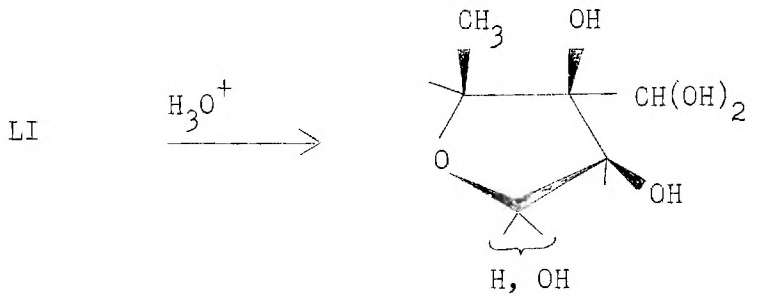
The exact nature of LI is not certain. Elemental analyses obtained for two samples of LI prepared in different ways are more satisfactory for a hydrate. The hydrate of LI would be expected to be soluble in water, but the solubility changes are more satisfactory for polymerization. The observation that the n.m.r. spectra of samples that had stood for one week were very poorly defined is consistent with polymer formation, since



Hydrate Polymer

a monomeric hydrate would be expected to show a resolved spectrum. While it is recognized that hydrate formation may occur under some conditions and polymer formation may occur under others, the general trend of the above evidence is for polymer formation.

Hydrolysis of the isopropylidene protecting group of LI was performed by stirring it with aqueous dioxane and Dowex 50W-X8 (H^+) for two days. After chromatography over carbon-celite, there was obtained a 67 per cent yield of L-streptose (LII), a colorless glass. Numerous attempts were made to crystallize this material without success.



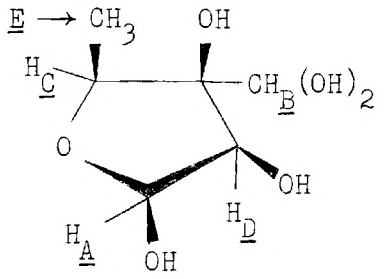
LII

Streptose gave an intense positive Benedict's test and showed a satisfactory infrared spectrum (Figure 17). Paper chromatography showed only one spot in both BEW (R_F 0.59, R_G 1.90) and EAW (R_F 0.39, R_G 2.78).

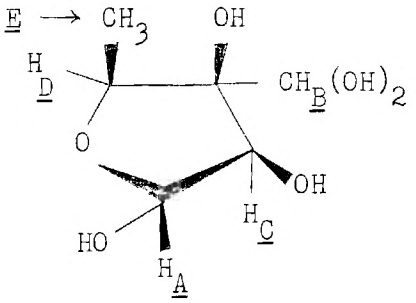
The n.m.r. spectrum (Figure 18) of streptose indicated the presence of two furanose isomers. The integration of the methyl group absorptions (8.5-8.9 τ) indicated that the two anomers were present in a ratio of approximately 79:21. Since the branched-chain aldehyde group can form only an energetically unfavored four-membered glycoside ring and since the branched-chain aldehyde hydrogen absorbs as a single peak in the region of absorption of glycosidic hydrogens (and not in the region of absorption of aldehydic protons, 0-1 τ), the branched-chain aldehyde function is probably hydrated. The simplicity of the n.m.r. spectrum,

the solubility in water, and the stability of the preparation all rule out the possibility of polymer formation. On the basis of the magnitude of the C_1-H, C_2-H coupling constants, the β anomer is probably present

β



α



H	τ	J, cps
	-β-	
A	4.77	AD = 4.1
B	4.97	CE = 6.5
C	5.55	
D	5.81	
E	8.73	
	-α-	
A	4.73	AC = 5.1
B	4.97	DE = 6.6
C	5.64	
D	5.75	
E	8.68	

LII

in largest amount. Because of the uncertainties previously mentioned, this assignment is not conclusive.

The calculation of the expected molecular rotations of the two anomers by Brewster's method (131) (assuming that the average conformation of the furanose ring is planar) gives a value of -22^0 for the β anomer and -149^0 for the α anomer (these are the same as predicted for dihydrostreptose since the method cannot distinguish between branched hydroxymethyl

or dihydroxymethyl groups). The calculated value for a mixture containing 79 per cent of the β anomer is -48^0 and for a mixture containing 79 per cent of the α anomer is -117^0. Because the observed molecular rotation value for the synthetic streptose is -32^0, the presence of 79 per cent of the β anomer is indicated. The assumptions made and the inherent uncertainty in this method make the assignment only tentative. Unfortunately, no data could be found in the literature for the composition of equilibrium mixtures of unprotected anomeric furanoses.

While other structures for streptose are possible, on the basis of the above evidence it is thought that anomeric C-4 furanose aldehyde hydrates (the structures shown as LII) exist in aqueous solution. It is likely that other structures of streptose exist in other solvents, since the n.m.r. spectrum of the compound in acetone-D_6 is very much more complicated than the deuterium oxide solution spectrum.

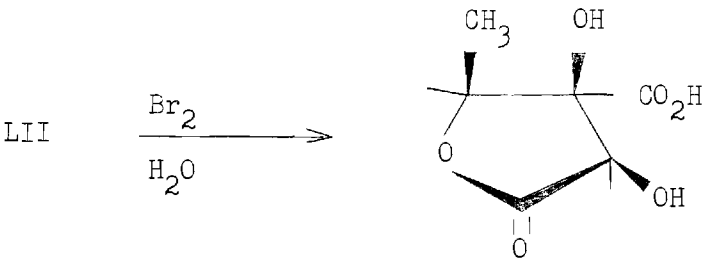
The production of maltol by the alkaline degradation of streptomycin involves the rearrangement of the streptose portion of the molecule (2). This reaction has been used as the basis of an assay procedure for streptomycin (11,141). A mechanism for the reaction has been proposed and it has been postulated that streptose must be present as a glycoside for this rearrangement to occur (2). This proposal was advanced because the alkaline treatment of streptomycin and methyl streptobiosaminide dimethyl acetal gave maltol, while under the same conditions tetraacetylstreptobiosamine and N-acetylstreptobiosamine did not (2).

When synthetic streptose was treated as previously described (141), no maltol was formed. However, 1,2-O-isopropylidene-3-C-formyl-5-deoxy-β-L-lyxofuranose (LI), under the same conditions, gave a positive test

for maltol. These results support the proposed requirement.

Regardless of the physical properties and expected structure of synthetic streptose, the most conclusive evidence for its identity would be the conversion into a known derivative that has been obtained by the degradation of streptomycin. The comparison of synthetic and authentic samples of such a derivative would furnish conclusive proof of the identity of the synthetic streptose.

Synthetic streptose, obtained as described above, was oxidized by bromine water and gave a 51 per cent yield of L-streptosonic acid monolactone (XIV). The product was very difficult to crystallize, as was previ-



XIV

ously observed (142). Only after all traces of water and other impurities had been removed could crystallization be effected. A sample* of syrupy authentic L-streptosonic acid monolactone obtained by the degradation of streptomycin was available and was similarly crystallized. While the physical properties of synthetic XIV differed slightly from those given in the literature (22), they agreed exceptionally well with those of the

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* The author is very grateful to Mr. R. K. Chawla for this sample.

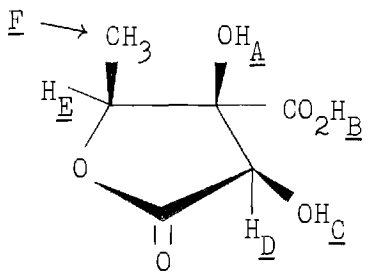
authentic XIV prepared in these laboratories. A comparison of the physical properties of the two samples and the literature values is given below.

Property	Synthetic XIV	Authentic XIV	Literature XIV (22)
m.p.	154-156°	154.5-156.5°	146-148°
$[\alpha]_D$	-41.1°	-40.8°	-37°
Elemental analysis:			
Calc'd.	Found		Found
C, 40.92	C, 40.88	----	C, 40.68
H, 4.58	H, 4.64	----	H, 4.21

The infrared spectra of synthetic XIV and authentic XIV are given as Figures 19 and 20, respectively. The infrared spectra of the two samples are identical.

The n.m.r. spectra of the two samples were identical with the exception of the position of the combination peak for the carboxyl and hydroxyl hydrogens. The position of this peak was observed to be concentration dependent, as expected.

The identity of the two samples was finally shown by the fact that a mixture of synthetic and authentic XIV melted at 153.5-155.5°. This value is not significantly depressed from the melting point of either sample. The identity of the two samples of L-streptosonic acid monolactone conclusively establishes the identity of the synthetic L-streptose. The agreement of the properties observed for the synthetic L-dihydrostreptosonic acid lactone and those given in the literature conclusively establishes the identity of the synthetic L-dihydrostreptose as well as furnishing further proof for the identity of the synthetic L-streptose.

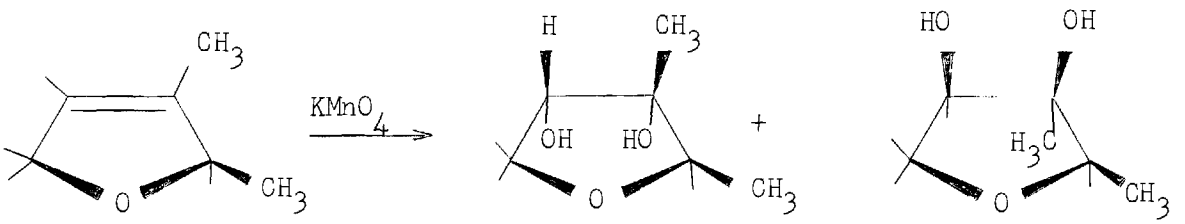


XIV

H	τ	J, cps
- Synthetic XIV -		
A,B,C,(16%)	3.85	EF = 6.5
A,B,C,(40%)	2.90	
D	5.05	
E	5.16	
F	8.67	
- Authentic XIV -		
A,B,C,(21%)	3.44	EF = 6.5
D	5.03	
E	5.13	
F	8.67	

Since the synthesis of streptose employed well-precedented reactions and since the stereochemistry at C_2 and C_4 of all the compounds is positively known, the synthesis provides conclusive proof of the overall structure of streptose and of the stereochemistry at C_2 and C_4. According to the precedents given and the structures of model and intermediate compounds, the stereochemistry at C_3 is strongly indicated to be as originally assigned.

Another method of proof for the configuration at C_3 in streptose has been pursued concurrently with this research (143). The hydroxylation of 2,3-dimethyl-2,5-dihydrofuran with potassium permanganate (known to give only cis dihydroxylation) gave as the minor product (as expected) dl-dideoxydihydrostreptose. The infrared and n.m.r. spectra and the GLC behaviors of the synthetic dl-X and a naturally derived sample of d-X were identical. Since this result conclusively shows that the C_2 and C_3 hydroxyl groups of X are cis and since the absolute stereochemistry at C_2



Major

(dl) (dl) (dl-X)

is proved by the synthesis of streptose, the total structures of streptose, and all of the derivatives given have been proved.

A Discussion of the Nuclear Magnetic Resonance Spectra of the Compounds Related to Streptose

The observation of regular trends in the variation (or lack thereof) of proton coupling constants and chemical shifts within a structurally related group of compounds is a very powerful method of organic structural analysis. The complete analysis of the n.m.r. spectra of the compounds prepared during this research should provide additional proof for both their structures and the structures of the final products.

The use of n.m.r. in structural determinations of carbohydrates has been developed extensively in recent years (108,144-158). Because of the general complexity of the interactions, an understanding of the conformation of each molecule is necessary. Karplus has derived an approximate expression for the relationship between the HCC'H' dihedral angle and the vicinal coupling constant, $J_{HH'}$, from theoretical valence-bond considerations (159,160). Among factors that were not included in this derivation are the effects of varying substituent electronegativity,

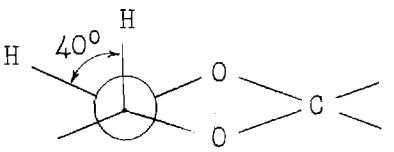
(161-166), carbon-carbon bond distance, and hybridization (160). In addition, the exact orientation of substituents has been claimed to have an effect on vicinal coupling constants (167). The importance of these additional factors seems to depend on the nature of the particular system being studied (165).

Several modifications of the Karplus equations have been made for use with carbohydrates (108,144,152,156,168). In view of the success of the modification advanced by Abraham et al. (108) in conformational investigations of carbohydrates and other compounds (154,156), this modification will be used throughout the following discussion. This relationship between vicinal coupling constants (J, cps) and dihedral angles (ϕ) is given below. Because of the present uncertainty regarding the effects of

$$J = 9.3 \cos^2 \phi - 0.28 \quad , \quad (0^\circ < \phi \leqslant 90^\circ)$$
$$J = 10.4 \cos^2 \phi - 0.28 \quad , \quad (90^\circ \leqslant \phi < 180^\circ)$$

substituents on the magnitude of vicinal coupling constants, the values given below for dihedral angles are regarded as approximate.

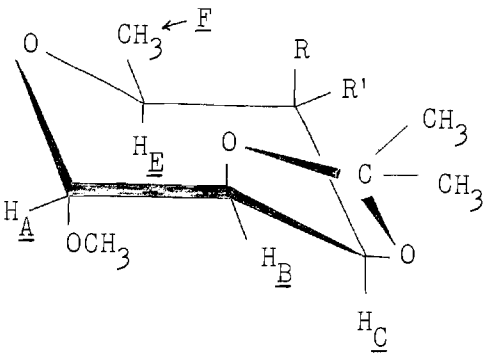
Recently it has been shown that five-membered cyclic acetal rings (1,3-dioxolanes) possess nonplanar conformations in solution (154,169). In every instance investigated the dihedral angle between the dioxolane ring hydrogens has been shown to be about 40° (154). This puckering would



be expected to impose some requirements on other rings to which acetals are usually attached in carbohydrates. Isopropylidene groups fused to pyranose rings have been shown to cause considerable distortion of the normal chair conformations (154,156). This effect is expected to be observed in most of the compounds prepared herein.

The n.m.r. spectra of some of the pyranose compounds prepared during the present research are summarized in Table 4. A significant feature of the spectra of these compounds is that coupling between the ano-

Table 4. A Summary of the n.m.r. Spectra of Some Pyranoses.



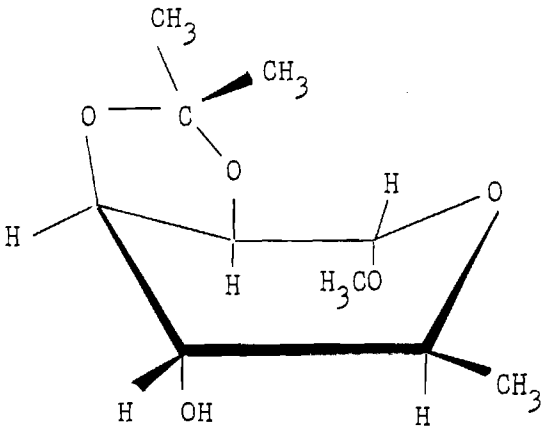
XVIII	R = H_D, R' = OH
XIX	R,R' = = O
XX	R,R' = = NOH
XXIII	R = OH, R' = $CH{=}CH_2$
XXVIII	R = $NH_3^+Cl^-$, R' = H_D
XLVIII	R = OH, R' = CHO

Compound	Chemical Shift (τ)						J, cps				
	A	B	C	D	E	F	AB	BC	CD	DE	EF
XVIII	5.30	6.15	6.01	6.04	6.61	8.79	0	5.9	0	0	6.0
XIX	5.15	5.56	5.56	----	5.74	8.60	0	0	-	-	6.9
XX	5.35	5.22	5.72	----	5.09	8.48	0	7.6	-	-	6.7
XXIII	5.03	5.89	5.89	----	6.24	8.82	0	0	-	-	6.7
XXVIII	4.87	5.26	5.13	5.91	6.62	8.62	0	6.1	1.4	11.0	6.8
XLVIII	5.20	6.02	5.63	----	6.29	8.93	0	7	-	-	7

meric proton (A) and the C_2 proton (B) is not observed. This indicates that the conformations of all of these compounds are similar (probably because of the rigidity imposed by the isopropylidene group).

The approximate conformation of XVIII can be obtained by an application of the methods given above. Since the AB, CD, and DE couplings

are not observed and since the protons involved show absorptions with different chemical shifts, it is concluded that the dihedral angles between these protons must be between 75° and 105°. The observed BC coupling of 5.9 cps indicates a dihedral angle of approximately 36°. This result is in good agreement with the previous observation that angles of about 40° are common such instances. Examination of a molecular model constructed according to the above data, indicates that the only conformation that would fit the angles given is a slightly skewed, unsymmetrically flattened boat form. Similar conformations have been obtained for other iso-

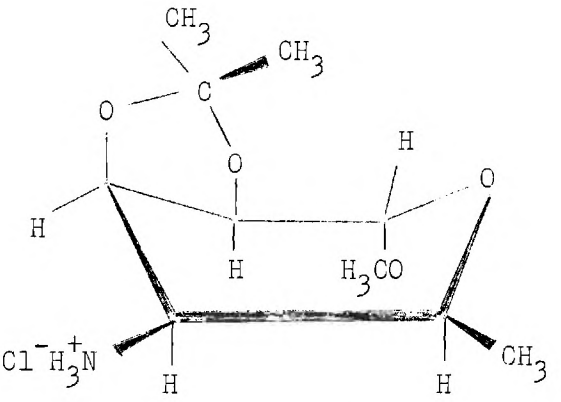


XVIII

propylidene pyranoses in the literature (154).

A more interesting example is compound XXVIII. Here the inversion at C_4 has resulted in CD and DE coupling. The indication that inversion has occurred is supported by the observed couplings. Since more ring couplings are observed for XXVIII than for XVIII, the conformation derived should be more meaningful. The dihedral angles indicated for XXVIII are:

AB, 75-105°; BC, ca. 34°; CD, ca. 65°; DE, 0° or 180°. The large coupling constant for DE (11.0 cps) is in agreement with similar values reported in the literature for vicinal hydrogens, one of which is attached to a carbon that has an ammonium substituent (165). Construction of a molecular model according to these data gives about the same conformation (a flattened boat form) for XXVIII as was obtained for XVIII.



XXVIII

Detailed examination of the n.m.r. spectra of XXIII and XLVIII confirms the talo configuration assigned to these compounds. Olefinic and carbonyl groups can exert diamagnetic anisotropic effects on nearby protons (170-172). Depending on the the exact geometry of the system, the absorptions of nearby protons can be shifted upfield or downfield. In Compound XXIII, if the vinyl group is oriented as required in the talo configuration, a downfield shift in the position of absorption of the C_5 proton is expected relative to that of XVIII. Furthermore, if the vinyl group were oriented such that the molecule had the manno configuration, the absorption of the terminal methyl group (C_6) would be shifted downfield.

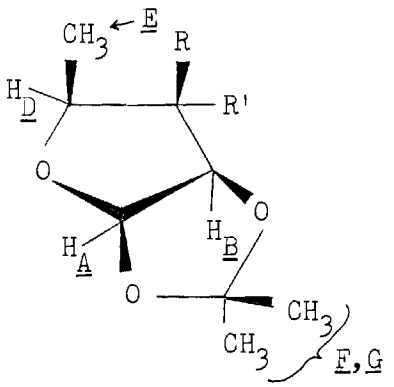
The observation that the absorption due to the C_5 proton is shifted downfield (6.61 to 6.24 τ) and that the C_6 protons are shifted slightly upfield (8.79 to 8.82 τ) confirms the configurational assignment. A similar analysis of XLVIII indicates that the same result is expected. Since for XLVIII the C_5 proton absorption is shifted downfield (6.61 to 6.29 τ) and the C_6 protons absorption is shifted slightly upfield (8.79 to 8.93 τ), the talo configuration of XXIII and XLVIII is further substantiated.

Conformational analysis of the furanose compounds prepared herein is considerably aided by the examples described in the literature (108, 148-151,155,157). If furanose rings were planar, coupling constants of 9 cps for cis (0° dihedral angle) and 2.3 cps for trans (120° dihedral angle) vicinal protons would be expected. The fact that furanose rings are seldom (if ever) planar has been amply demonstrated.

Since the modified Karplus equation used herein was derived for furanoses, it is expected that this relationship will provide a good description of their conformations (108,154,155). Table 5 contains a summary of the n.m.r. spectra of some of the furanoses prepared herein.

The spectra of XXXII and the derivatives of its free hydroxyl function (XXXV, XXXVI, XXXVII) are consistent in the lack of BC coupling and the magnitude of the AB coupling. The dihedral angles indicated by the ring couplings in this series are: AB, ca. 46°; BC, 75-105°; CD, 54-62° or 117-125°. Examination of a model constructed according to these values indicates that the best conformation is achieved by deforming C_2 above and C_3 below the plane formed by C_1-O-C_4. This result is in agreement with the conclusions reached by Abraham and co-workers from an n.m.r. analysis of 13 similar 1,2-O-isopropylidene furanoses (108,155).

Table 5. A Summary of the n.m.r. Spectra of Some Furanoses.



XXXII R = $H_{\underline{C}}$, R' = OH

XXXV R = $H_{\underline{C}}$, R' = O-(benzoyl)

XXXVI R = $H_{\underline{C}}$, R' = O-(3,5-dinitrobenzoyl)

XXXVII R = $H_{\underline{C}}$, R' = O-(p-toluenesulfonyl)

XLI R,R' = =O

XLII R,R' = =NOH

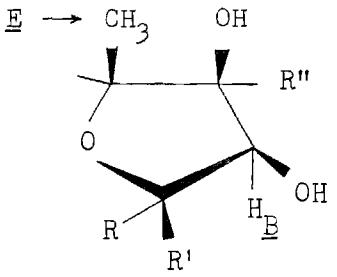
XLIII R = OH, R' = $CH{=}CH_2$

XLIV R = OH, R' = CH_3

XLIX R = OH, R' = CH_2OH

LI R = OH, R' = CHO

Compound	Chemical Shift (τ)							J, cps			
	A	B	C	D	E	F	G	AB	BC	CD	DE
XXXII	4.12	5.47	5.96	5.95	8.61	8.47	8.68	4.1	0	2.6	6.8
XXXV	4.02	5.28	4.81	5.67	8.49	8.43	8.68	4.2	0	1.8	7.0
XXXVI	4.03	5.15	4.75	5.59	8.47	8.41	8.62	4.2	0	1.8	7.0
XXXVII	4.18	5.39	5.41	5.83	8.70	8.51	8.73	4.1	0	2.8	6.9
XLI	4.02	5.53	----	5.77	8.55	8.50	8.59	4.4	-	---	7.2
XLII	4.13	5.11	----	5.02	8.43	8.41	8.62	4.0	-	---	6.7
XLIII	4.29	5.60	----	6.13	8.73	8.38	8.62	4.5	-	---	6.7
XLIV	4.31	5.79	----	6.20	8.69	8.40	8.71	4.3	-	---	6.7
XLIX	4.26	5.46	----	6.13	8.67	8.38	8.61	4.5	-	---	7.1
LI	4.23	5.38	----	5.93	8.69	8.36	8.56	4.3	-	---	6.5



α-LII R = OH, R' = $H_{\underline{A}}$, R'' = $CH_{\underline{C}}(OH)_2$

β-LII R = $H_{\underline{A}}$, R' = OH, R'' = $CH_{\underline{C}}(OH)_2$

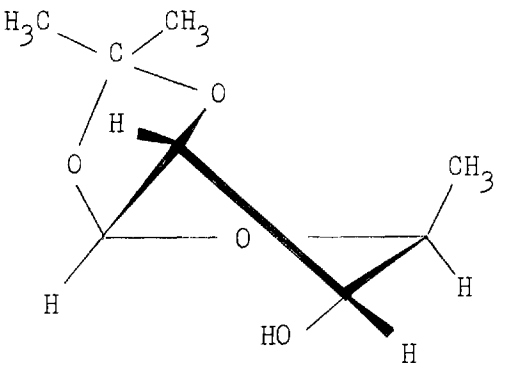
α-L R = OH, R' = $H_{\underline{A}}$, R'' = $CH_{2(\underline{C})}OH$

β-L R = $H_{\underline{A}}$, R' = OH, R'' = $CH_{2(\underline{C})}OH$

XIV R,R' = =O, R'' = CO_2H

XV R,R' = =O, R'' = $CH_{2(\underline{C})}OH$

Compound	A	B	C	D	E	AB	DE
α-LII	4.73	5.64	4.97	5.75	8.68	5.1	6.6
β-LII	4.77	5.81	4.97	5.55	8.73	4.1	6.5
α-L	4.76	5.82	6.38	5.91	8.71	5.1	6.6
β-L	4.72	5.85	6.38	5.65	8.76	3.8	6.6
XIV	----	5.05	----	5.16	8.67	---	6.5
XV	----	5.38	6.38	5.37	8.67	---	6.5



XXXII

Since only $J_{\underline{AB}}$ is observed in the spectra of the ketone XLI and the ketoxime XLII, a similar conformational analysis is not possible for these compounds. An interesting feature is that the B and D protons absorb at considerably lower field in the oxime (XLII) than in the ketone (XLI). Since the diamagnetic anisotropic effects for ketones and oximes are similar (170), the ring conformation of the oxime may be different from that of the ketone.

The spectra of the 1,2-O-isopropylidene furanose compounds that have the lyxo configuration (XLIII, XLIV, XLIX, LI) show several consistent features: the anomeric protons (A) absorb at slightly higher field than those of the arabino compounds (XXXII, XXXV, XXXVI, XXXVII), the AB coupling constants are slightly larger than those of the arabino compounds, and the positions of absorption of the E protons are remarkably constant (8.70 $\pm$ 0.03 τ). The vinyl compound (XLIII) does not show significant downfield shifts of either the B and D protons on one side of the ring or of the E and F or G protons on the other side. Inspection of molecular models indicates that in the lyxo configuration the vinyl

group would be free to rotate, thus averaging anisotropic effects on the B and D protons. In the arabino configuration the vinyl group cannot freely rotate because of severe nonbonding interactions with the terminal methyl group and the isopropylidene group; thus the vinyl group would be expected to cause downfield shifts in the absorptions of the E and F or G protons.

A more important observation in support of the lyxo configuration of these compounds is the remarkable constancy of the absorption position of the E and F or G protons. If the arabino configuration was present, this absorption would be expected to be shifted downfield in XLIII and LI (anisotropic effects) and not shifted in XLIX and XLIV. Since in the lyxo configuration the changes in the nature of the branched-chain group are occurring on the other side of the ring, no large changes would be expected in the absorptions of the E and F or G protons.

The observation that the anomeric protons of the 1,2-O-isopropylidene furanose compounds absorb about one τ unit lower than those of the pyranose compounds can be explained on the basis of ring current effects (173,174). Ring currents in cyclic saturated compounds are responsible for the fact that equatorial protons of cyclohexane-like rings absorb at lower field than axial ones (173-175). It is observed that, in the pyranose series, the anomeric protons are equatorial to only one ring. In the 1,2-O-isopropylidene furanose series ring currents in both the tetrahydrofuran and 1,3-dioxolane rings can contribute to the deshielding of the anomeric protons. While the orientation of the 1,2-O-isopropylidene furanose anomeric protons is not exactly equatorial, the puckering of the two fused rings forces the anomeric proton into a position that is more

analogous to an equatorial location than an axial one. In support of this explanation, the observed positions of absorption of the anomeric protons of α- and β-L and α- and β-LII (which do not have isopropylidene groups) are only slightly lower than those of the pyranoses (4.7-4.8 τ versus 4.9-5.3 τ).

Because only one ring coupling constant is observed for the lyxo compounds, conformational analyses analogous to those made above are not possible. However, the conformation of the 1,2-O-isopropylidene-lyxo-furanoses is indicated by both the positions of absorption of the A protons and J_{AB}. Since for these compounds, the A protons all absorb at higher field than the arabino ones (compounds XXXII, XXXV, XXXVI, and XXXVII), their orientation must have less equatorial character. This is probably caused by a decrease in the amount of puckering of the tetrahydrofuran ring. Partial flattening of this ring would also decrease the AB dihedral angle (since this angle is 0° in the planar conformation). This decrease in dihedral angle would be expected to be accompanied by an increase in J_{AB}; which is observed (arabino J_{AB} = 4.1 ± 0.1, lyxo J_{AB} = 4.4 ± 0.1). Even though these changes are small, they consistently indicate that the 1,2-O-isopropylidene-lyxo-furanose rings are slightly less puckered than the 1,2-O-isopropylidene-arabino-furanose rings. Since the lyxo compounds have a hydroxyl substituent on the same side of the ring as the methyl and isopropylidene groups, steric repulsion may be responsible for this flattening of the ring.

The consistency of the absorption position of the isopropylidene methyl groups (F, 8.43 ± 0.08 τ; G, 8.63 ± 0.08 τ) indicates their remoteness from the center of the structural differences of these compounds.

Because of this constancy, exact assignments would be highly tentative.

The second portion of Table 5 summarizes the n.m.r. spectra of the anomers of streptose (LII) and dihydrostreptose (L), as well as those of streptosonic acid monolactone (XIV) and dihydrostreptosonic acid lactone (XV). The most striking feature of these spectra is the lack of significant variation in the position of absorption of the E protons (8.72 ± 0.05 τ). In addition, the B and D protons of XIV absorb at lower field than those of XV. Examination of molecular models indicates that the diamagnetic anisotropic effect of the branched-chain carboxyl group of XIV is probably responsible for the shift. Since the E protons absorption position is fairly constant, the observed shifts further substantiate the assigned lyxo configuration. Because only one ring coupling constant is observed in these compounds, and they do not have a rigid fused ring system, conformational analysis is not possible.

In general, the spectra of the compounds prepared herein support many of the previously published conclusions. In particular, the observed couplings between vicinal protons on carbons that form a part of 1,3-dioxolane rings support the assigned puckered conformations of such rings (154,169).

CHAPTER IV

CONCLUSIONS

L-Streptose, L-dihydrostreptose, and a number of related compounds have been synthesized. The identities of synthetic streptose and dihydrostreptose have been shown by their conversion in good yield to L-streptosonic acid monolactone (XIV) and L-dihydrostreptosonic acid lactone (XV), respectively. Compound XIV was shown to be identical to a naturally derived sample of L-streptosonic acid monolactone by a rigorous comparison of their physical and spectral properties. Compound XV was conclusively identified by a comparison of physical and spectral properties with values obtained from the literature.

All of the previously unknown compounds and derivatives prepared were thoroughly characterized by means of their physical properties and infrared and n.m.r. spectra. Satisfactory elemental analyses were obtained for all solid compounds. These data support the structures assigned to the intermediates and to the final products.

The synthetic pathway used did not alter the absolute configuration at C_2 and C_4 of either the starting material or any of the intermediate compounds. Therefore, the absolute configurations at C_2 and C_4 of streptose have been proved to be identical to those of the starting 1,2-O-isopropylidene-5-deoxy-β-L-arabinofuranose and are D(S) and L(R), respectively.

That the absolute configuration at C_3 of L-streptose is D(R) is demonstrated by the expected course of the reactions used, a study of the

reactions of certain model compounds, and the n.m.r. spectra of the intermediate compounds related to streptose. These results, together with the synthesis of dideoxydihydrostreptose by potassium permanganate hydroxylation of 2,3-dimethyl-2,5-dihydrofuran in these laboratories (143), prove that the configuration at C_3 of streptose is D(R). Therefore, the structure of streptose has been proved to be 3-C-formyl-5-deoxy-L-lyxose, as previously assigned.

The synthesis of streptose completes the synthetic proof of structure of streptomycin except for the glycosidic linkages. The results of this research have been published in communication form (176).

In addition to the synthesis of L-streptose, the synthesis of a new amino sugar, 4-amino-4,6-dideoxy-L-talose and the synthesis of a new derivative of 5-deoxy-L-arabinose, 2,3-O-isopropylidene-5-deoxy-L-arabinose diethyl dithioacetal were also accomplished.

LITERATURE CITED*

(1) S. A. Waksman, E. Bugie, and A. Schatz, Proc. Soc. Exptl. Biol. Med., 55, 66 (1944); S. A. Waksman and A. Schatz, J. Am. Pharm. Assoc., 34, 273 (1945).

(2) R. U. Lemieux and M. L. Wolfrom, Advances in Carbohydrate Chem., 3, 357-384 (1948), and references cited therein.

(3) "The Merck Index," 7th ed., Merck and Co. Inc., Rahway, N. J., 1960, p. 981.

(4) S. A. Waksman, "The Actinomycetes," The Williams and Wilkins Co., Baltimore, Md., Vol. 1, 1959, pp. 233-236.

(5) N. G. Brink, F. A. Kuehl, Jr., and K. Folkers, Science, 102, 506 (1945).

(6) A. Bondi, C. C. Dietz, and E. H. Spauldine, ibid., 103, 399 (1946).

(7) J. Fried and O. Wintersteiner, J. Am. Chem. Soc., 69, 79 (1947).

(8) M. W. Miller, "The Pfizer Handbook of Microbial Metabolites," McGraw-Hill, New York, 1961, p. 39.

(9) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, and K. Folkers, J. Am. Chem. Soc., 68, 2557 (1946).

(10) D. P. Young, J. Chem. Soc., 1961, 1337.

(11) J. R. Schenck and M. A. Spielman, J. Am. Chem. Soc., 67, 2276 (1945).

(12) I. R. Hooper, L. H. Klemm, W. J. Polglase, and M. L. Wolfrom, ibid., 68, 2120 (1946).

(13) H. G. Fletcher, Jr., Advances in Carbohydrate Chem., 3, 60 (1948).

(14) O. Wintersteiner and A. Klingsberg, J. Am. Chem. Soc., 73, 2917 (1951).

(15) M. L. Wolfrom, S. M. Olin, and W. J. Polglase, ibid., 72, 1724 (1950).

---

* For the complete titles of all journals referred to see Chemical Abstracts, 50, 1 J (1956).

(16) F. A. Kuehl, Jr., R. L. Peck, C. E. Hoffhine, Jr., E. W. Peel, and K. Folkers, ibid., 69, 1234 (1947); 70, 2325 (1948).

(17) J. R. Dyer and A. W. Todd, ibid., 85, 3896 (1963).

(18) F. A. Kuehl, Jr., E. H. Flynn, N. G. Brink, and K. Folkers, ibid., 68, 2096 (1946).

(19) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, and K. Folkers, ibid., 70, 2085 (1948).

(20) F. A. Kuehl, Jr., E. H. Flynn, F. W. Holly, R. Mozingo, and K. Folkers, ibid., 68, 546 (1946); 69, 3032 (1947).

(21) N. G. Brink, F. A. Kuehl, Jr., E. H. Flynn, and K. Folkers, ibid., 68, 2405 (1946).

(22) F. A. Kuehl, Jr., E. H. Flynn, N. G. Brink, and K. Folkers, ibid., 68, 2679 (1946).

(23) F. A. Kuehl, Jr., R. L. Clark, M. N. Bishop, E. H. Flynn, and K. Folkers, ibid., 71, 1445 (1949).

(24) J. Fried, D. E. Walz, and O. Wintersteiner, ibid., 68, 2746 (1946).

(25) M. L. Wolfrom and C. W. DeWalt, ibid., 70, 3148 (1948).

(26) M. L. Wolfrom, M. J. Cron, C. W. DeWalt, and R. M. Husband, ibid., 76, 3675 (1954).

(27) J. R. Dyer, private communication.

(28) L. J. Heuser, M. A. Dolliver, and E. T. Stiller, J. Am. Chem. Soc., 75, 4013 (1953).

(29) I. J. McGilveray and J. B. Stenlake, Chem. and Ind., 1964, 238.

(30) Wang Yu, Loh Hsi-Yien, Lin Wen-Teh, and Chang Chi-Hsien, Acta Chim. Sinica, 25, 257 (1959).

(31) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co. Inc., New York, N. Y., 1960, p. 242.

(32) F. P. Treadwell and W. T. Hall, "Analytical Chemistry," John Wiley and Sons Inc., New York, N. Y., 1942, Vol. II, p. 606.

(33) H. B. Hayes, M.S. Thesis, Georgia Institute of Technology, 1959, pp. 12-15.

(34) J. T. Edward and D. M. Waldron, J. Chem. Soc., 1952, 3631.

(35) E. Pascu, T. P. Mora, and P. W. Kent, Science, 110, 446 (1949).

(36) University of Texas Publication No. 5109, University of Texas, Austin, Texas, 1951.

(37) R. F. Nassar, Ph.D. Thesis, Georgia Institute of Technology, 1964, p. 18.

(38) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," John Wiley and Sons Inc., New York, N. Y., 1957, p. 112.

(39) Reference 38, p. 102.

(40) E. E. Percival and E. G. V. Percival, J. Chem. Soc., 1950, 690.

(41) P. A. Levene and I. E. Muskat, J. Biol. Chem., 105, 431 (1934).

(42) W. T. Haskins, R. M. Hahn, and C. S. Hudson, J. Am. Chem. Soc., 68, 628 (1946).

(43) E. Fischer, Ber., 28, 1158 (1895).

(44) P. A. Levene and J. Compton, J. Am. Chem. Soc., 57, 2306 (1935).

(45) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, ibid., 75, 422 (1953).

(46) Reference 3, p. 632.

(47) P. A. Robins and J. Walker, J. Chem. Soc., 1952, 642.

(48) E. Fischer, Ber., 27, 673 (1894).

(49) E. L. Patterson, R. Milstrey, and E. L. R. Stokstad, J. Am. Chem. Soc., 78, 5868 (1956).

(50) D. L. MacDonald in R. L. Whistler and M. L. Wolfrom, ed.'s, "Methods in Carbohydrate Chemistry," Academic Press Inc., New York, N. Y., Vol. I, 1962, p. 74.

(51) Reference 32, Vol. I, p. 287; Vol. II, p. 738.

(52) Org. Syntheses, Collective Vol. III, John Wiley and Sons Inc., New York, N. Y., 1955, p. 619.

(53) L. Hough and T. J. Taylor, J. Chem. Soc., 1955, 3544.

(54) Reference 50, p. 75.

(55) P. A. Levene and J. Compton, J. Biol. Chem., 116, 189 (1936).

(56) A. K. Mitra and P. Karrer, Helv. Chim. Acta, 38, 1 (1955).

(57) R. S. Tipson, M. A. Clapp, and L. H. Cretcher, J. Org. Chem., 12, 133 (1947)

(58) Reference 38, p. 111.

(59) E. A. Braude and E. R. H. Jones, J. Chem. Soc., 1945, 498.

(60) J. Meisenheimer and W. Theilacker, Ann., 493, 33 (1931)

(61) Reference 38, p. 156.

(62) F. A. Kuehl, Jr., in R. L. Whistler and M. L. Wolfrom, ed.'s, "Methods in Carbohydrate Chemistry," Academic Press Inc., New York, N. Y., Vol. I, 1962, pp. 268-272.

(63) Org. Syntheses, 40, 93 (1960).

(64) C. C. Sweeley, R. Bentley, M. Makita, and W. W. Wells, J. Am. Chem. Soc., 85, 2497 (1963).

(65) H. G. Jones, J. K. N. Jones, and M. B. Perry, Can. J. Chem., 40, 1559 (1962).

(66) H. W. Kirchner in R. L. Whistler and M. L. Wolfrom ed.'s, "Methods in Carbohydrate Chemistry," Academic Press Inc., New York, N. Y., Vol. I, 1962, pp. 13-20.

(67) A. Assarsson and O. Theander, Acta Chem. Scand., 12, 1507 (1958), and references cited therein.

(68) J. R. Holum, J. Org. Chem., 26, 4814 (1961), and references cited therein.

(69) E. Walton, J. O. Rodin, C. H. Stammer, F. W. Holly, and K. Folkers, J. Am. Chem. Soc., 80, 5168 (1958).

(70) J. S. Burton, W. G. Overend, and N. R. Williams, Chem. and Ind., 1961, 175.

(71) P. M. Collins and W. G. Overend, ibid., 1963, 375.

(72) W. G. Overend, ibid., 1963, 342.

(73) R. K. Chawla, private communication.

(74) S. Patton, J. Biol. Chem., 184, 130 (1950).

(75) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p. 238.

(76) D. J. Cram and K. R. Kopecky, J. Am. Chem. Soc., 81, 2748 (1959).

(77) D. J. Cram and D. R. Wilson, ibid., 85, 1245 (1963), and references cited therein.

(78) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p. 69.

(79) W. A. Bonner, Advances in Carbohydrate Chem., 6, 251-289 (1951).

(80) M. L. Wolfrom and S. Hanessian, J. Org. Chem., 27, 1800 (1962).

(81) M. L. Wolfrom and S. Hanessian, ibid., 27, 2107 (1962).

(82) J. S. Burton, W. G. Overend, and N. R. Williams, Proc. Chem. Soc., 1962, 181.

(83) Org. Syntheses, 39, 10 (1959).

(84) Reference 31, p. 154.

(85) J. R. Dyer, Methods of Biochem. Anal., Vol. 3, 111, Interscience, Inc., New York, 1956.

(86) J. D. Dutcher, Advances in Carbohydrate Chem., 18, 259-308 (1963).

(87) A. B. Foster and D. Horton, Advances in Carbohydrate Chem., 14, 213-281 (1959).

(88) R. W. Wheat, E. L. Rollins, and J. M. Leatherwood, Biochem. Biophys. Res. Commun., 9, 120 (1962).

(89) C. L. Stevens, P. Blumbergs, F. A. Daniher, R. W. Wheat, A. Kujomoto, and E. L. Rollins, J. Am. Chem. Soc., 85, 3061 (1963).

(90) C. L. Stevens, P. Blumbergs, D. H. Otterbach, J. L. Strominger, M. Matsuhashi, and D. N. Dietzler, ibid., 86, 2937 (1964).

(91) C. L. Stevens, P. Blumbergs, F. A. Daniher, J. L. Strominger, M. Matsuhashi, D. N. Dietzler, S. Suzuki, T. Okazaki, K. Sugimoto, and R. Okazaki, ibid., 86, 2939 (1964).

(92) J. S. Brimacombe and M. J. How, Chem. and Ind., 1962, 1382.

(93) C. W. Shoppee and R. J. Stephenson, J. Chem. Soc., 1954, 2230.

(94) M. L. Wolfrom, J. Bernsmann, and D. Horton, J. Org. Chem., 27, 4505 (1962), and references cited therein.

(95) E. J. Reist, R. R. Spencer, and B. R. Baker, ibid., 24, 1618 (1959).

(96) R. W. Jeanloz and A. M. C. Rapin, ibid., 28, 2978 (1963).

(97) B. R. Baker and H. S. Sachdev, ibid., 28, 2132 (1963).

(98) A. K. Bose, J. F. Kistner, and L. Farber, ibid., 27, 2925 (1962).

(99) E. J. Reist, R. R. Spencer, B. R. Baker, and L. Goodman, Chem. and Ind., 1962, 1794.

(100) E. Fischer, Ber., 29, 1381 (1896).

(101) V. Deulofeu, J. Chem. Soc., 1930, 2602.

(102) F. Micheel, Ber., 63, 347 (1930).

(103) E. R. deLabriola and V. Deulofeu, J. Org. Chem., 12, 726 (1947).

(104) P. Andrews, L. Hough, and J. K. N. Jones, J. Am. Chem. Soc., 77, 125 (1955).

(105) E. L. Patterson, R. Milstrey, and E. L. R. Stokstad, ibid., 78, 5868 (1956).

(106) R. Kuhn, W. Bister, and W. Dafeldecker, Ann., 617, 115 (1958).

(107) D. L. MacDonald and H. O. L. Fischer, Biochem. Biophys. Acta, 12, 203 (1953).

(108) R. J. Abraham, L. D. Hall, L. Hough, and K. A. McLauchlan, J. Chem. Soc., 1962, 3699.

(109) L. M. Jackman, "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, 1959, p. 55.

(110) J. R. Dyer, "Applications of Absorption Spectroscopy of Organic Compounds," Prentice-Hall Inc., Englewood Cliffs, N. J., 1965, pp. 87,88.

(111) Reference 52, p. 207.

(112) H. Adkins, R. M. Elofson, A. G. Rossow, and C. C. Robinson, J. Am. Chem. Soc., 71, 3622 (1949), and references cited therein.

(113) K. Heyns and H. Paulsen, Advances in Carbohydrate Chem., 17, 169-221 (1962), and references cited therein.

(114) Reference 113, pp. 173-181.

(115) S. A. Barker and E. J. Bourne, Advances in Carbohydrate Chem., 7, 177 (1952), and references cited therein.

(116) M. M. Baizer, J. Org. Chem., 25, 670 (1960).

(117) H. R. Nace and J. J. Monagle, ibid., 24, 1792 (1959).

(118) A. P. Johnson and A. Pelter, J. Chem. Soc., 1964. 520.

(119) N. Kornblum, W. J. Jones, and G. J. Anderson, J. Am. Chem. Soc., 81, 4113 (1959).

(120) K. E. Pfitzner and J. G. Moffatt, ibid., 85, 3027 (1963).

(121) V. J. Traynelis and W. L. Hergenrother, ibid., 86, 298 (1964).

(122) J. Hine, "Physical Organic Chemistry," McGraw-Hill Inc., New York, N. Y., 2nd edition, 1963, p. 184.

(123) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons Inc., New York, N. Y., Vol. 2, 1961, pp. 1053-1054.

(124) P. J. Beynon, P. M. Collins, and W. G. Overend, Proc. Chem. Soc., 1964, 342.

(125) D. Horton and D. H. Hutson, Advances in Carbohydrate Chem., 18, 123-199 (1963), and references cited therein.

(126) R. U. Lemieux, Can. J. Chem., 29, 1079 (1951).

(127) M. L. Wolfrom and A. Thompson, J. Am. Chem. Soc., 56, 880 (1934).

(128) G. Slomp, Jr., and J. L. Johnson, ibid., 80, 915 (1958).

(129) B. Witkop and J. B. Patrick, ibid., 74, 3855 (1952).

(130) J. B. Patrick and B. Witkop, J. Org. Chem., 19, 1824 (1954).

(131) J. H. Brewster, J. Am. Chem. Soc., 81, 5475, 5483, 5493 (1959).

(132) O. L. Chapman and R. W. King, ibid., 86, 1256 (1964).

(133) R. J. Ouellette, ibid., 86, 4378 (1964).

(134) B. Casu, M. Reggiani, G. G. Gallo, and A. Vigevani, Tetrahedron Letters, No. 39, 2839 (1964).

(135) D. G. Easterby, L. Hough, and J. K. N. Jones, J. Chem. Soc., 1951, 3416.

(136) O. Westphal, H. Feier, O. Luderitz, and I. Fromme, Biochem. Z., 326, 139 (1954).

(137) P. S. Bailey, Chem. Rev., 58, 925 (1958), and references cited therein.

(138) A. L. Henne and P. Hill, J. Am. Chem. Soc., 65, 752 (1943).

(139) E. J. Corey and H. J. Burke, ibid., 78, 174 (1956).

(140) W. F. Symes and C. R. Dawson, ibid., 75, 4952 (1953).

(141) G. E. Boxer, V. C. Jelinek, and P. M. Leghorn, J. Biol. Chem., 169, 153 (1947).

(142) F. A. Kuehl, Jr., private communication.

(143) K. C. Rice, private communication.

(144) R. W. Lenz and J. P. Heeschen, J. Polymer Sci., 51, 247 (1961), and references cited therein.

(145) Reference 75, p. 395 ff.

(146) R. U. Lemieux, R. K. Kullnig, and R. Y. Moir, J. Am. Chem. Soc., 80, 2237 (1958).

(147) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, ibid., 80, 6098 (1958).

(148) C. D. Jardetzky, ibid., 82, 229 (1960).

(149) C. D. Jardetzky, ibid., 83, 2919 (1961).

(150) C. D. Jardetzky, ibid., 84, 62 (1962).

(151) R. U. Lemieux, Can. J. Chem., 39, 116 (1961).

(152) R. U. Lemieux and J. W. Lown, ibid., 42, 893 (1964).

(153) R. U. Lemieux and R. Nagarajan, ibid., 42, 1270 (1964).

(154) B. Coxon and L. D. Hall, Tetrahedron, 20, 1685 (1964), and references cited therein.

(155) R. J. Abraham, K. A. McLauchlan, L. D. Hall, and L. Hough, Chem. and Ind., 1962, 213.

(156) L. D. Hall, L. Hough, K. A. McLauchlan, and K. Pachler, ibid., 1962, 1465.

(157) L. D. Hall, ibid., 1963, 950.

(158) L. D. Hall and L. Hough, Proc. Chem. Soc., 1962, 382.

(159) M. Karplus, J. Chem. Phys., 30, 11 (1959).

(160) M. Karplus, J. Am. Chem. Soc., 85, 2870 (1963).

(161) R. E. Glick and A. A. Bothner-By, J. Chem. Phys., 25, 362 (1956).

(162) T. Schaefer, Can. J. Chem., 40, 1 (1962).

(163) R. J. Abraham and K. G. R. Pachler, Mol. Phys., 6, 165 (1963).

(164) P. Laszlo and P. R. Schleyer, Bull. Soc. Chim. France, 1964, 87.

(165) A. C. Huitric, J. B. Carr, W. F. Trager, and B. J. Nist, Tetrahedron, 19, 2145 (1963).

(166) K. L. Williamson, J. Am. Chem. Soc., 85, 516 (1963).

(167) D. H. Williams and N. S. Bhacca, ibid., 86, 2742 (1964).

(168) K. L. Williamson and W. S. Johnson, ibid., 83, 4623 (1961).

(169) R. U. Lemieux, J. D. Stevens, and R. R. Fraser, Can. J. Chem., 40, 1955 (1962).

(170) Reference 110, pp. 77,78.

(171) Reference 75, p. 176 ff.

(172) Reference 109, pp. 122,129.

(173) Reference 110, pp. 82,83.

(174) Reference 75, pp. 183,389.

(175) F. R. Jensen, D. S. Noyce, C. H. Sederholm, and A. J. Berlin, J. Am. Chem. Soc., 84, 386 (1962).

(176) J. R. Dyer, W. E. McGonigal, and K. C. Rice, J. Am. Chem. Soc., 87, 654 (1965).

APPENDIX

Table 6. Index of Figures.

Figure Number	Compound Number	Figure Page	Text Discussion Page
1	XIX	168	84-86,147
2	XXIII	168	90-92,147,149
3	XXVIII	169	94,96,97,147-149
4	XXIX	169	98,99
5	XXXII	170	102-104,150,151
6	XXXV	170	104,105,150,151
7	XXXVI	171	105-107,150,151
8	XXXVII	171	105-107,150,151
9	XLI	172	116-118,150-152
10	XLI	172	116-118,150-152
11	XXXIX	173	110-112
12	XLIV	173	121,122,151-154
13	XLIII	174	119,120,151-154
14	XLIX	174	126,127,151-154
15	L	175	127-129,151,154,155
16	L	175	127-129,151,154,155
17	LII	176	139-141,151,154,155
18	LII	176	139-141,151,154,155
19	XIV	177	142-144,151,155
20	XIV	177	142-144,151,155

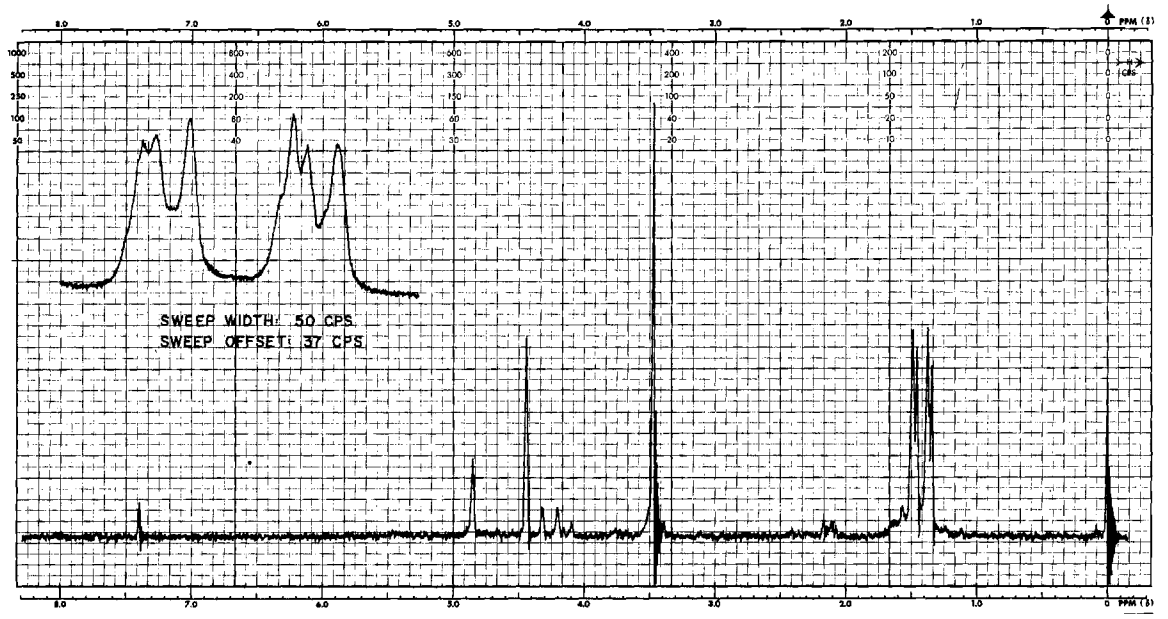


Figure 1. The Nuclear Magnetic Resonance Spectrum of Methyl 2,3-O-Isopropylidene-6-deoxy-α-L-lyxo-hexopyranos-4-ulose.

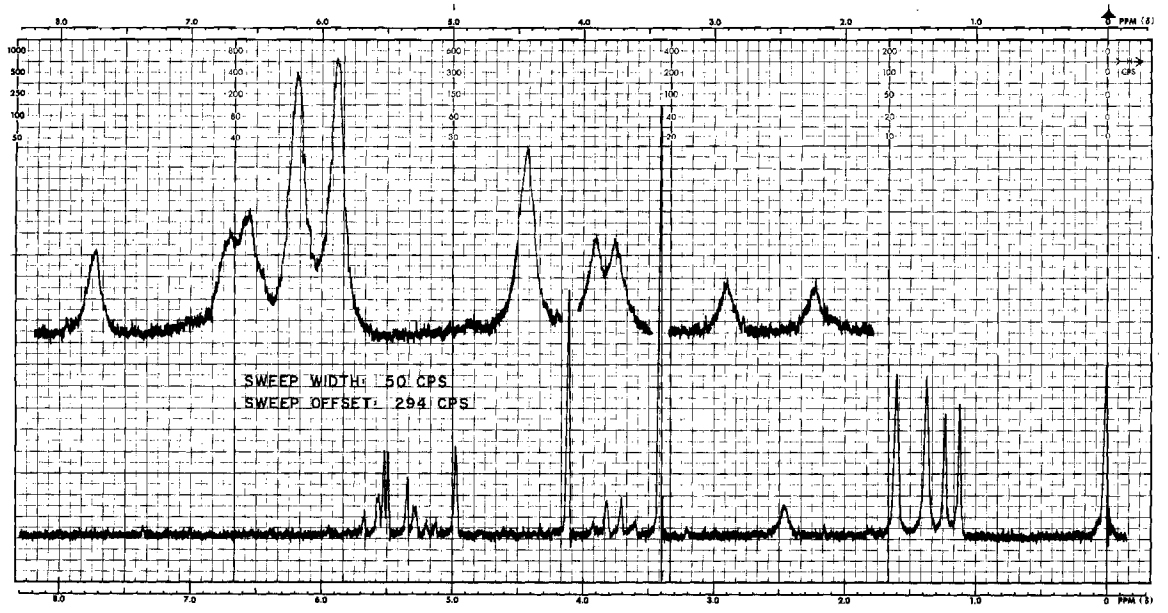


Figure 2. The Nuclear Magnetic Resonance Spectrum of Methyl 2,3-O-Isopropylidene-4-C-vinyl-6-deoxy-α-L-talopyranoside.

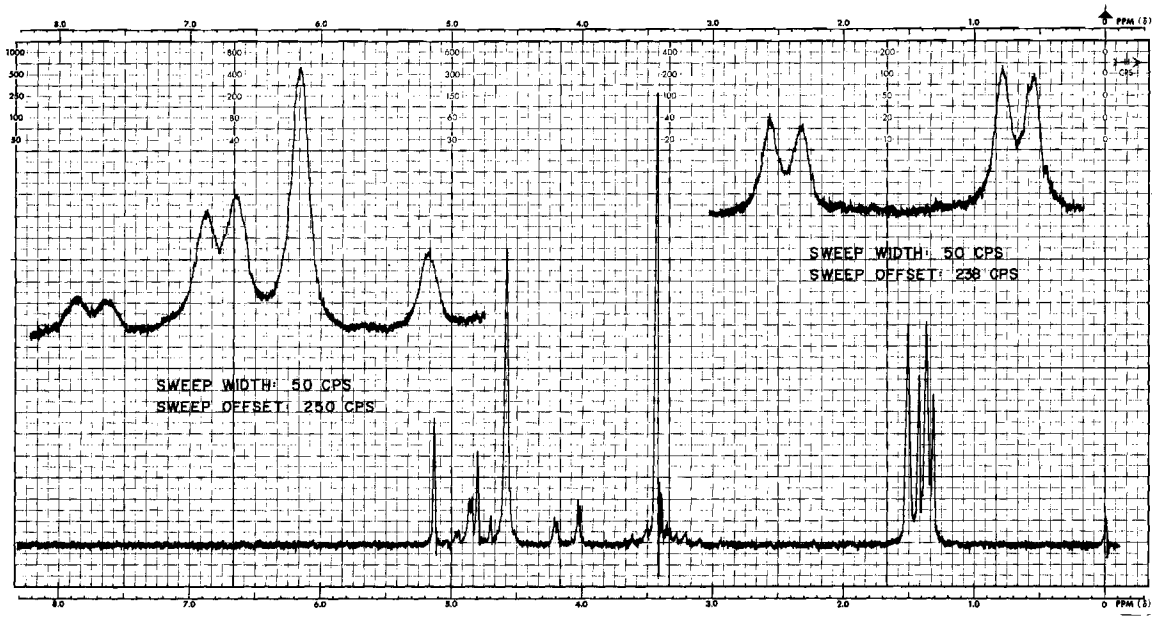


Figure 3. The Nuclear Magnetic Resonance Spectrum of Methyl 2,3-O-Isopropylidene-4-amino-4,6-dideoxy-α-L-talopyranoside Hydrochloride.

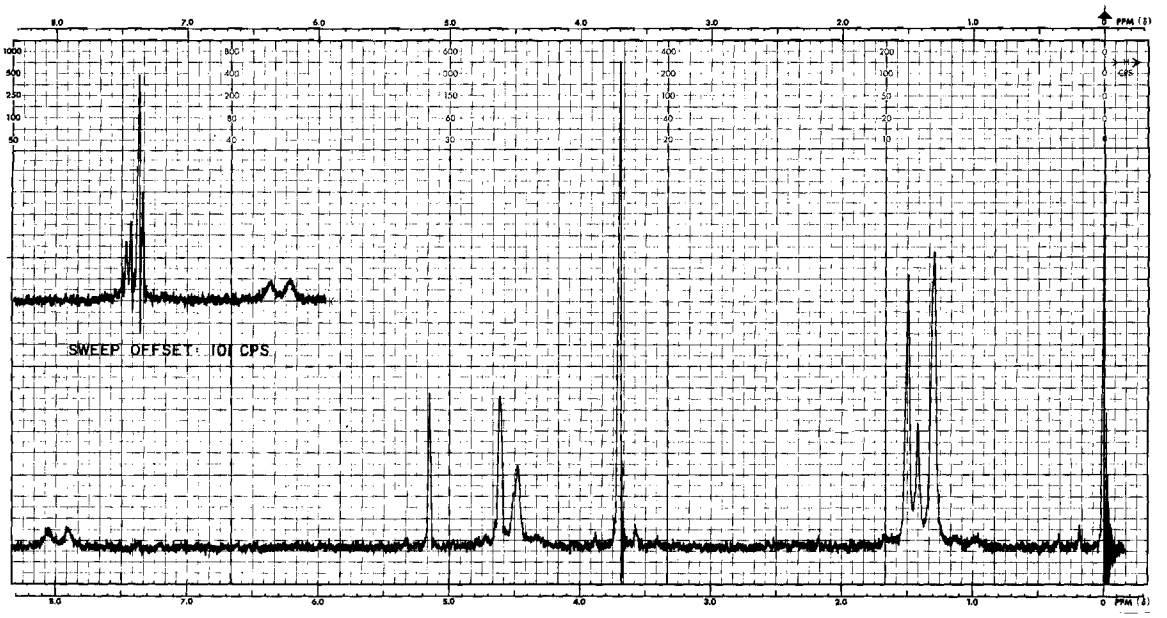


Figure 4. The Nuclear Magnetic Resonance Spectrum of Methyl 2,3-O-Isopropylidene-4-C-(3,5-dinitrobenzamido)-4,6-dideoxy-α-L-talopyranoside.

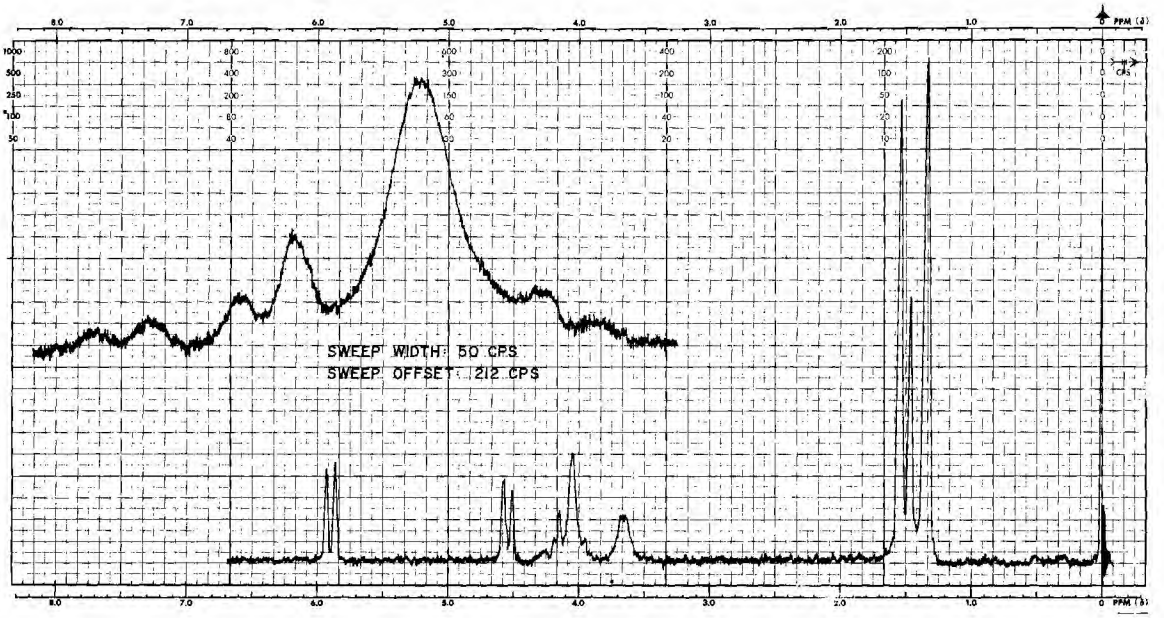


Figure 5. The Nuclear Magnetic Resonance Spectrum of 1,2-O-Isopropylidene-5-deoxy-β-L-arabinofuranose.

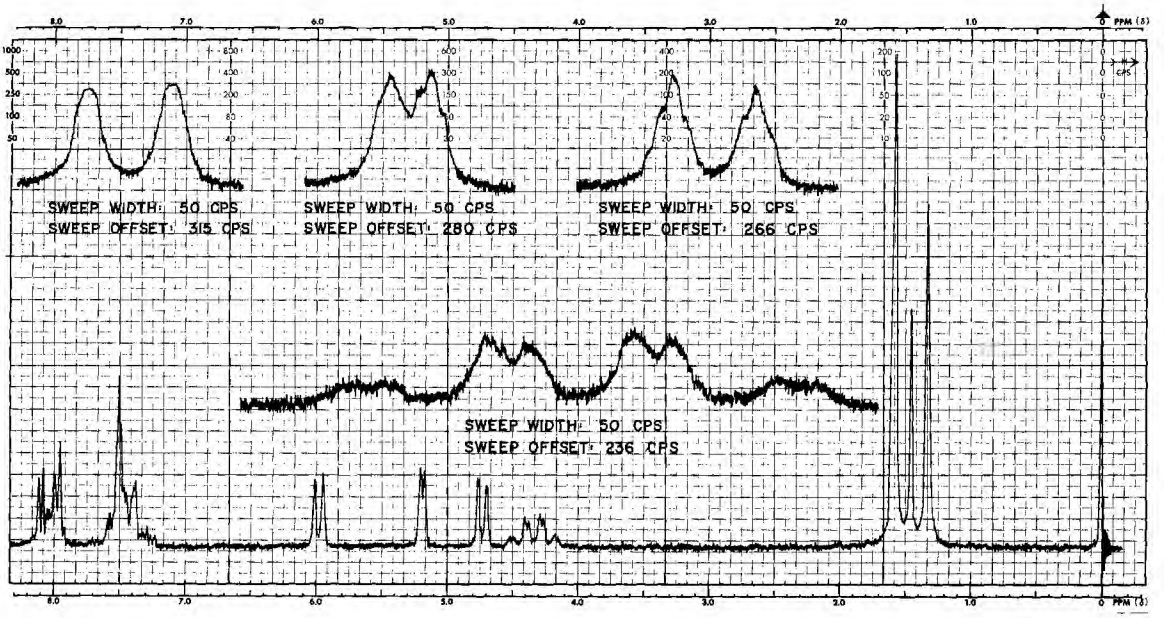


Figure 6. The Nuclear Magnetic Resonance Spectrum of 1,2-O-Isopropylidene-3-O-benzoyl-5-deoxy-α-L-arabinofuranose.

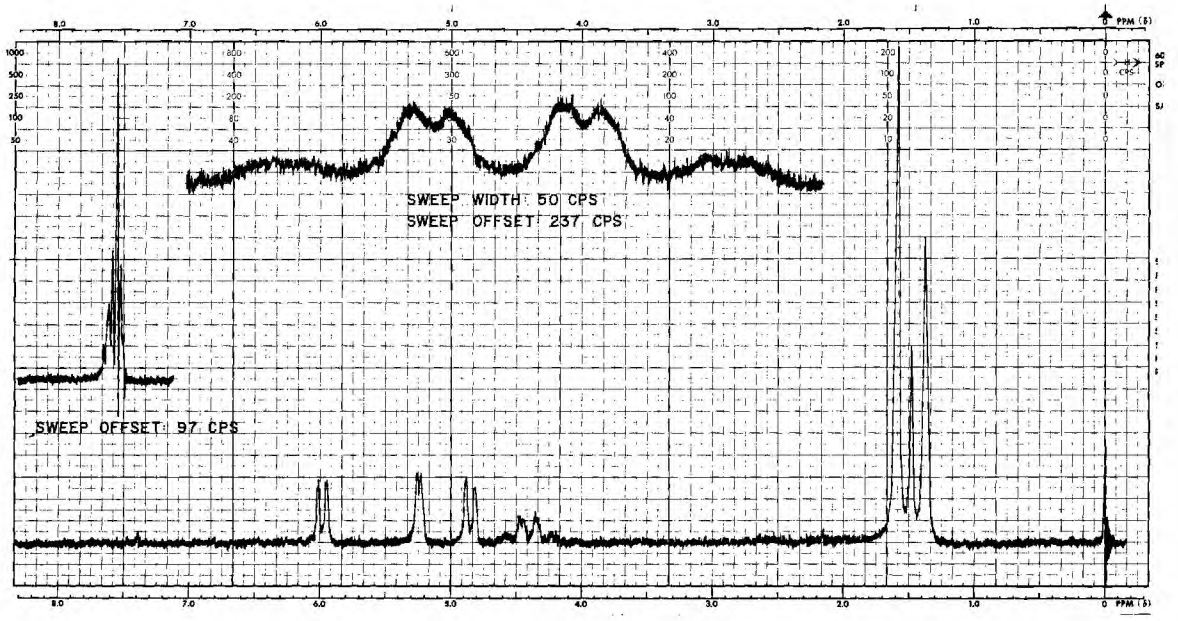


Figure 7. The Nuclear Magnetic Resonance Spectrum of 1,2-O-Isopropylidene-3-O-(3,5-dinitrobenzoyl)-5-deoxy-β-L-arabinofuranose.

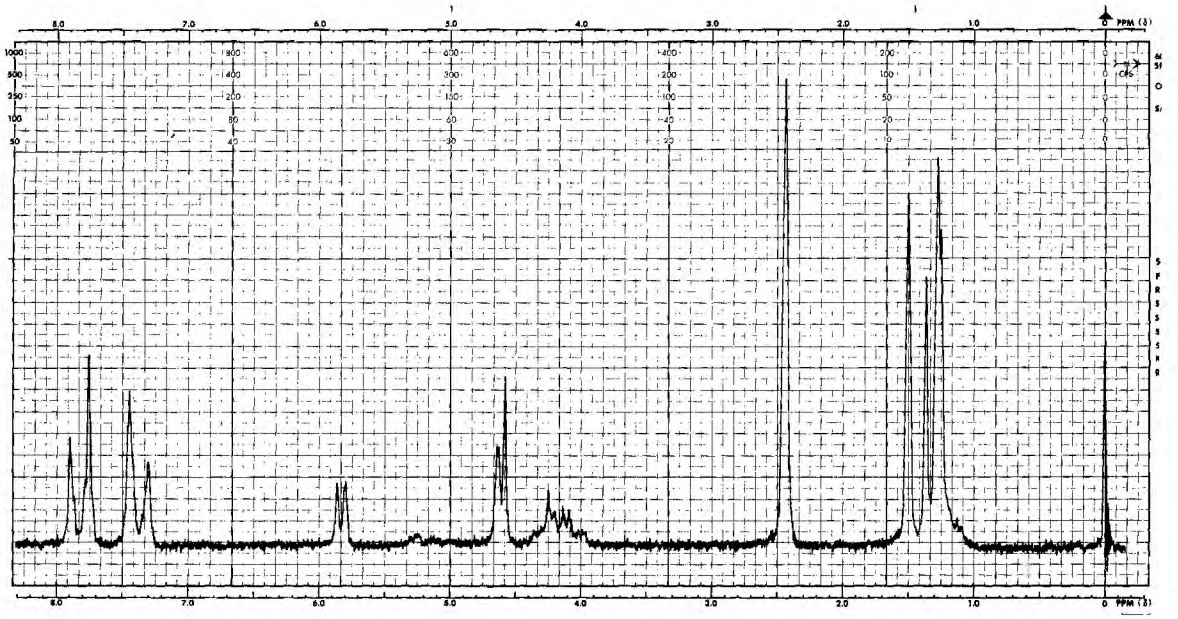


Figure 8. The Nuclear Magnetic Resonance Spectrum of 1,2-O-Isopropylidene-3-O-(p-toluenesulfonyl)-5-deoxy-β-L-arabinofuranose.

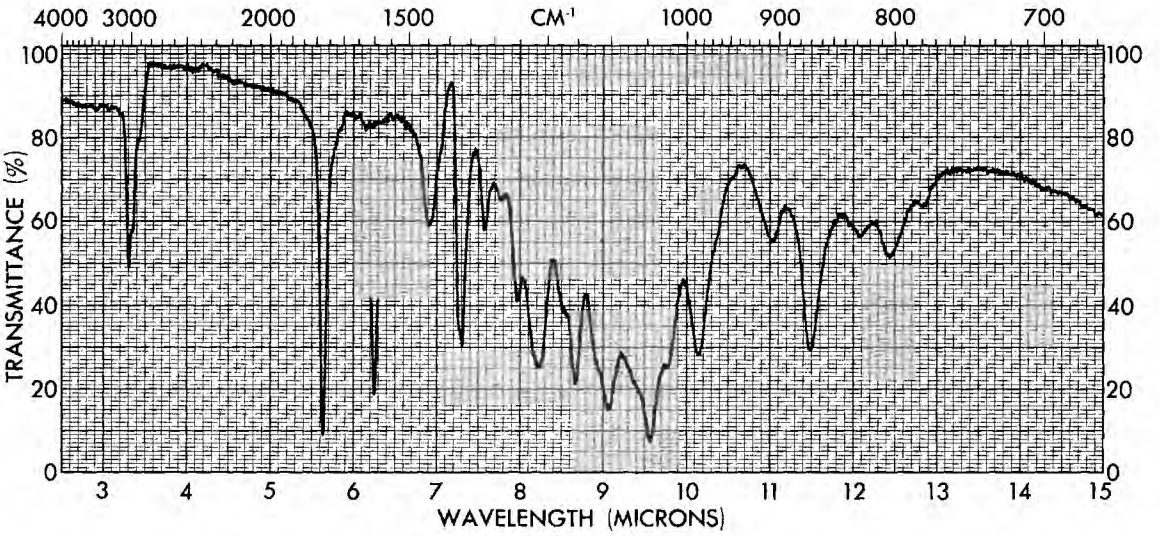


Figure 9. The Infrared Spectrum of 1,2-O-Isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose.

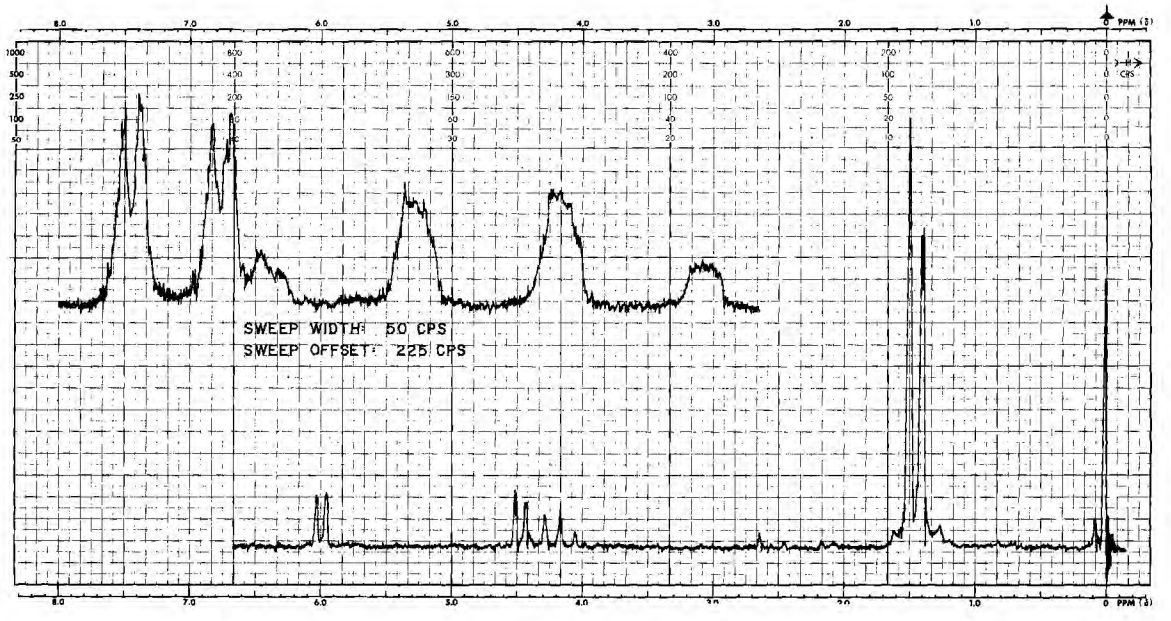


Figure 10. The Nuclear Magnetic Resonance Spectrum of 1,2-O-Isopropylidene-5-deoxy-β-L-threo-pentofuranos-3-ulose.

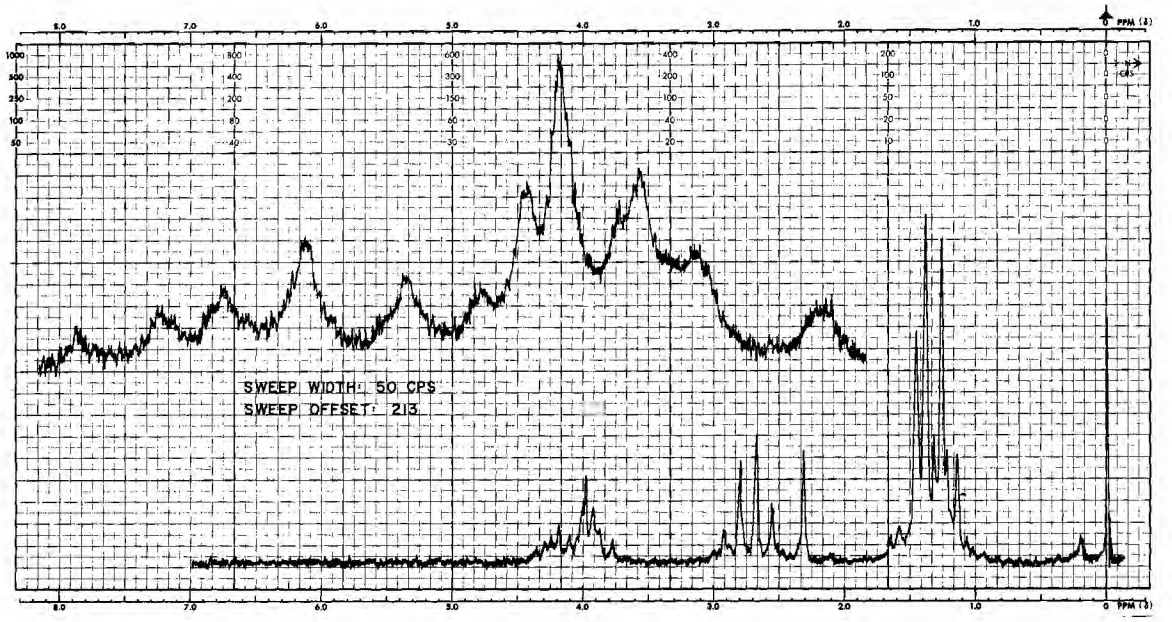


Figure 11. The Nuclear Magnetic Resonance Spectrum of 2,3-O-Isopropylidene-5-deoxy-L-arabinose Diethyl Dithioacetal.

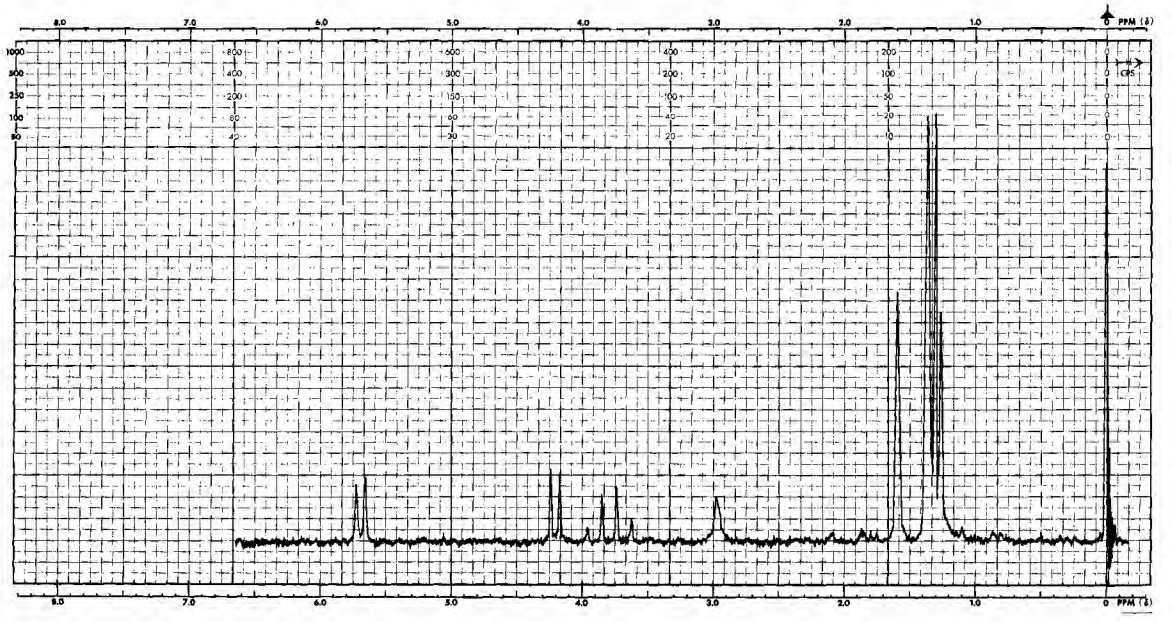


Figure 12. The Nuclear Magnetic Resonance Spectrum of 1,2-O-Isopropylidene-3-C-methyl-5-deoxy-β-L-lyxofuranose.

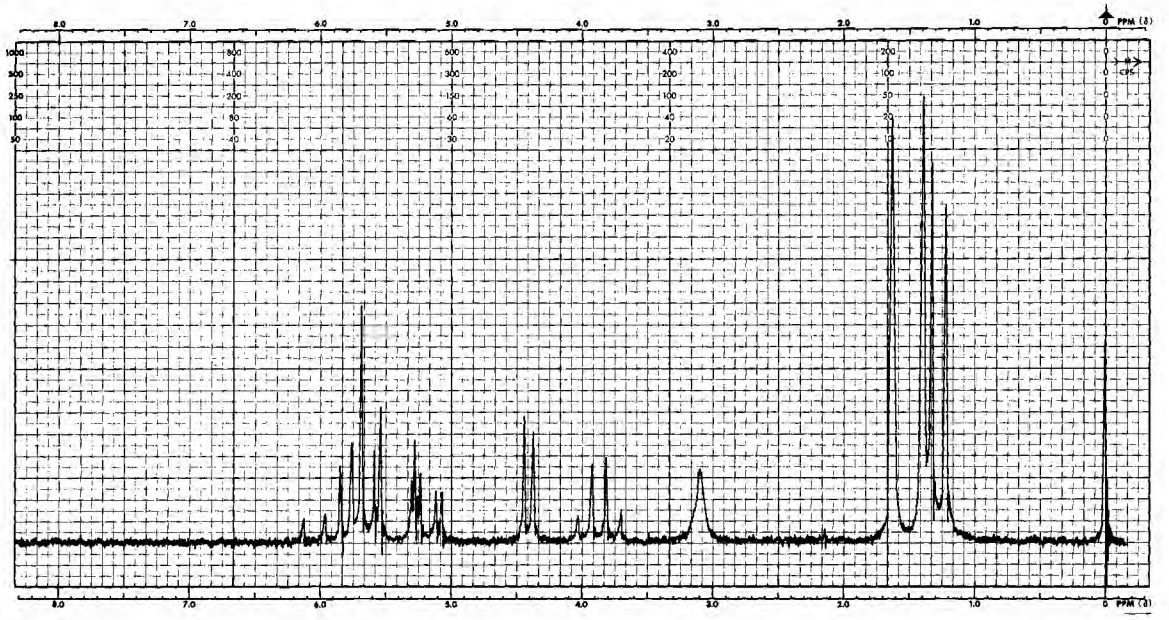


Figure 13. The Nuclear Magnetic Resonance Spectrum of 1,2-O-Isopropylidene-3-C-vinyl-5-deoxy-β-L-lyxofuranose.

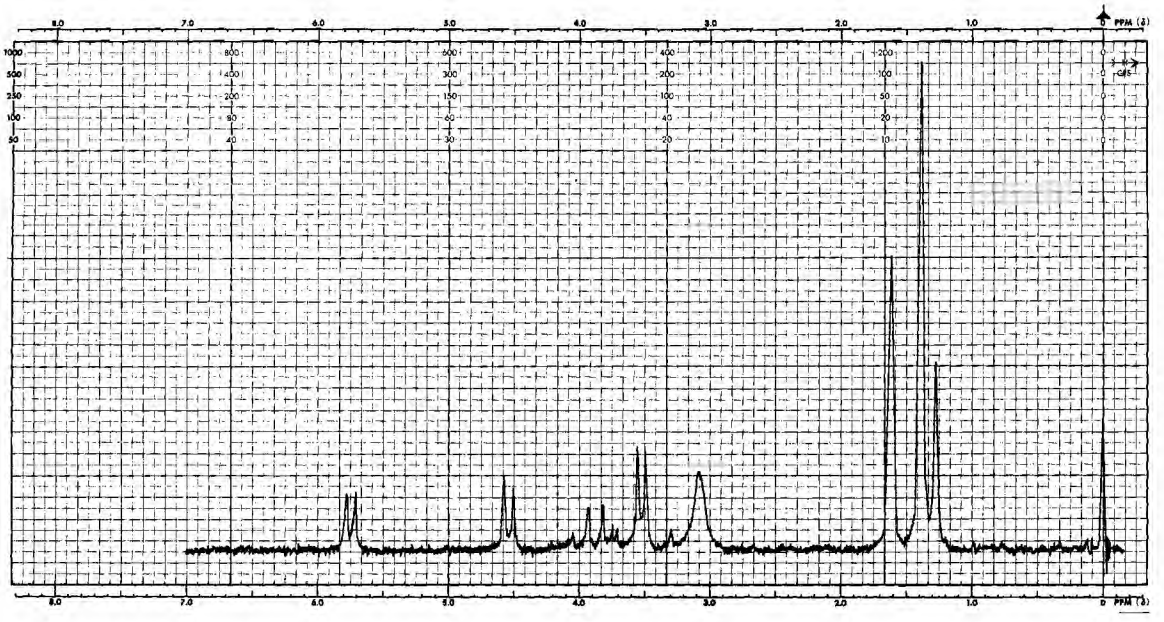


Figure 14. The Nuclear Magnetic Resonance Spectrum of 1,2-O-Isopropylidene-3-C-hydroxymethyl-5-deoxy-β-L-lyxofuranose.

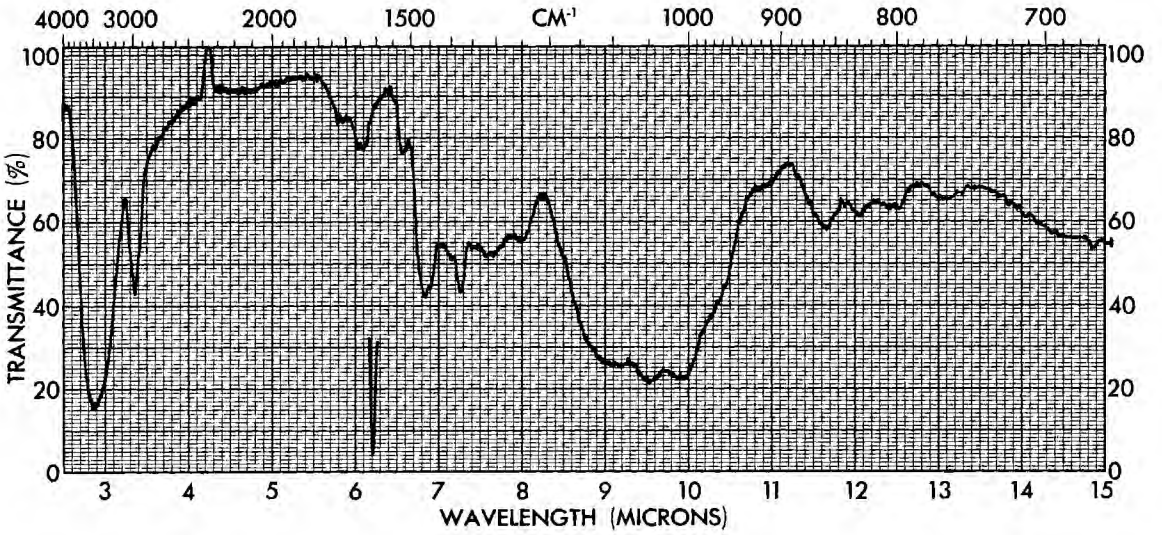


Figure 15. The Infrared Spectrum of L-Dihydrostreptose.

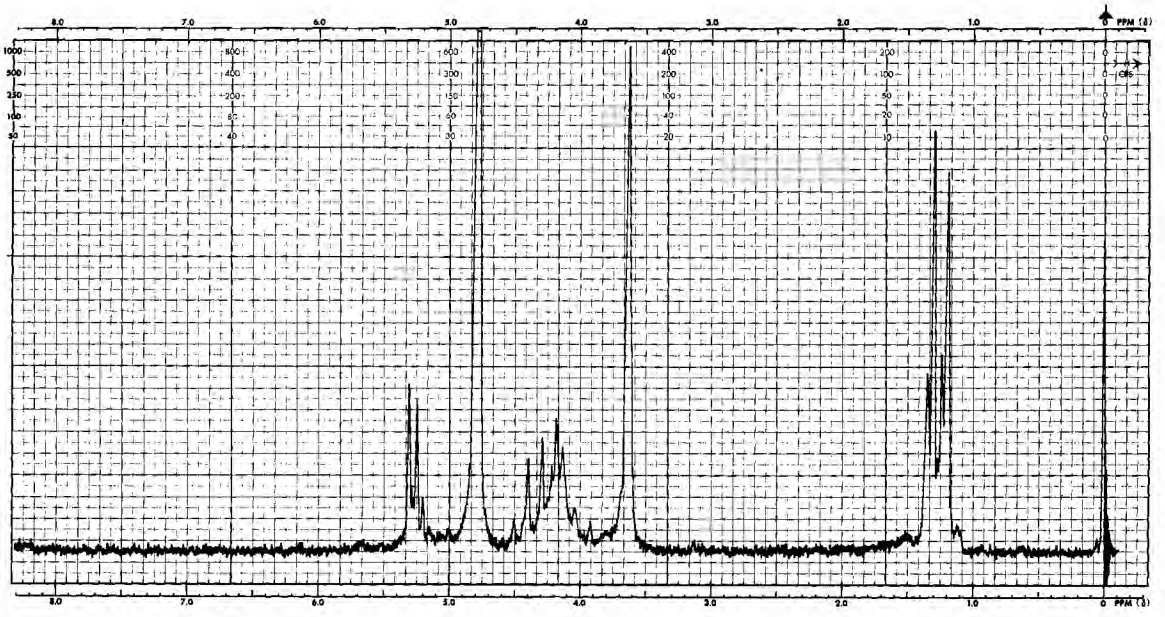


Figure 16. The Nuclear Magnetic Resonance Spectrum of L-Dihydrostreptose.

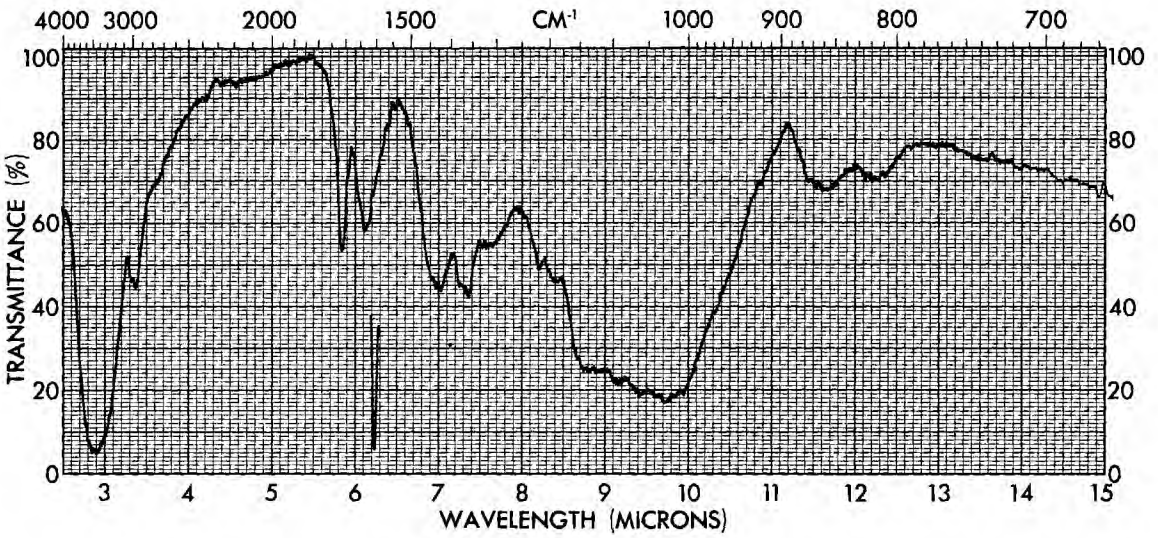


Figure 17. The Infrared Spectrum of L-Streptose.

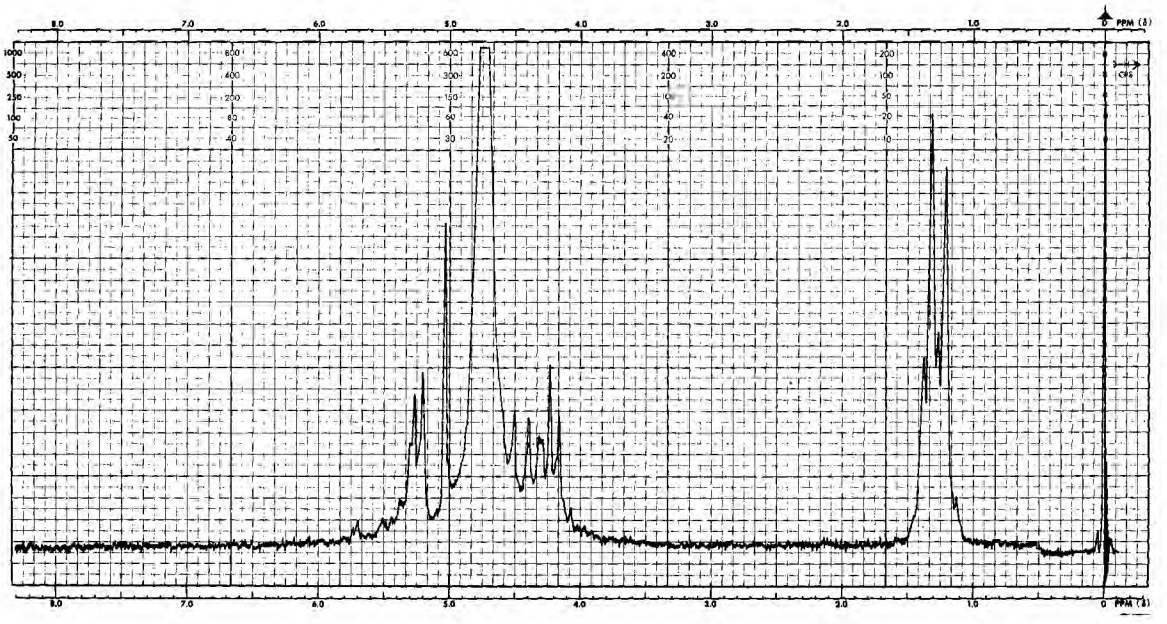


Figure 18. The Nuclear Magnetic Resonance Spectrum of L-Streptose.

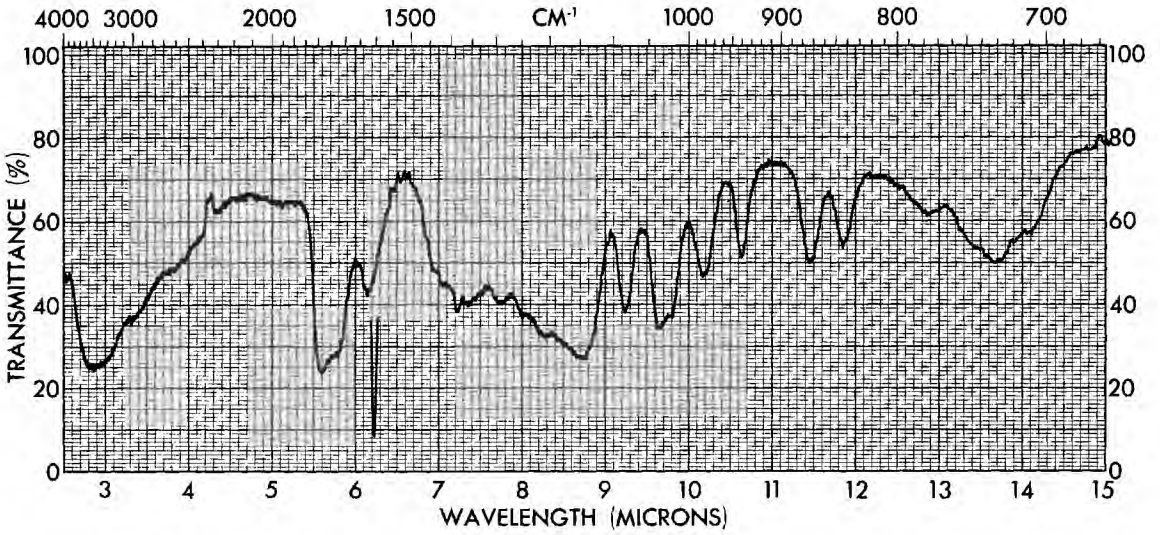


Figure 19. The Infrared Spectrum of Synthetic L-Streptosonic Acid Monolactone.

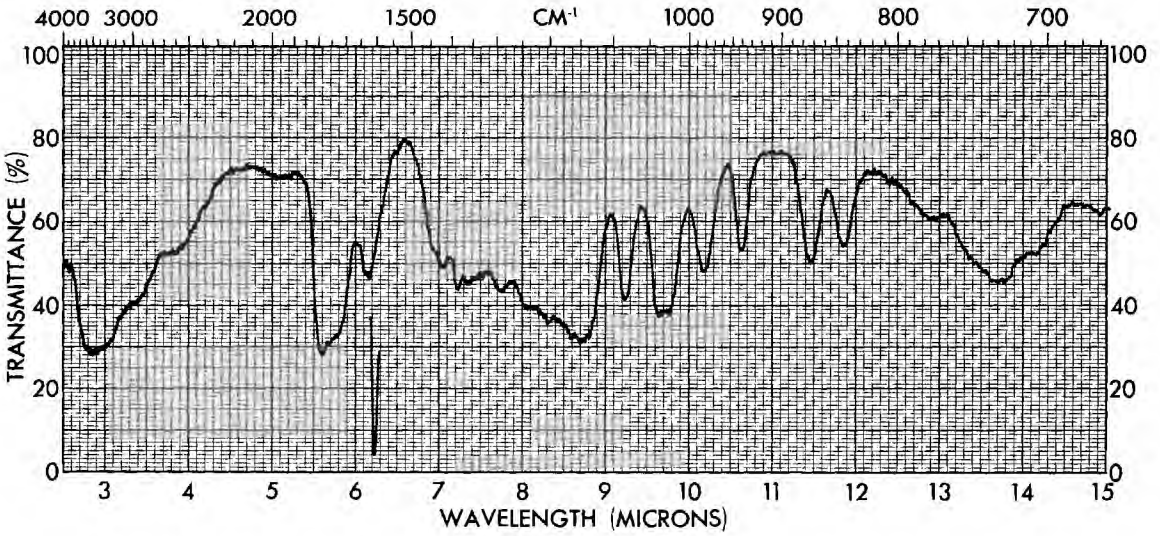


Figure 20. The Infrared Spectrum of Authentic L-Streptosonic Acid Monolactone.

VITA

William Edward McGonigal was born August 20, 1939, in Decatur, Georgia. He attended E. L. Connally Elementary School and J. E. Brown High School in Atlanta, Georgia. He entered the Georgia Institute of Technology in September, 1957, and in June, 1961 was graduated with a Bachelor of Science degree in Chemistry. During the summer of 1960, he received a National Science Foundation Undergraduate Research Participation Award. He began graduate study at the Georgia Institute of Technology in June, 1961 and in September, 1962 was awarded a National Institutes of Health Predoctoral Fellowship.

He was married on June 13, 1959 to Sarah Ann Bowers, and has one child, William Edward, Jr.